Modeling metabolic networks

(1)Cellular networks (examples)
(2)General questions
(3)Theoretical approaches

Introduction

(4)Why metabolic networks?
(5)Basic aspects

Some facts

(6)Experimental protocol
(7)Genome-scale models

Problems

(8)Steady-state theory (FBA)
(9)Optimized steady states
(10)Generalized steady states and
(11)Maximum growth theory (VN)
(12)The “shape” of metabolism
(13)Its response to perturbations
(14)Open problems

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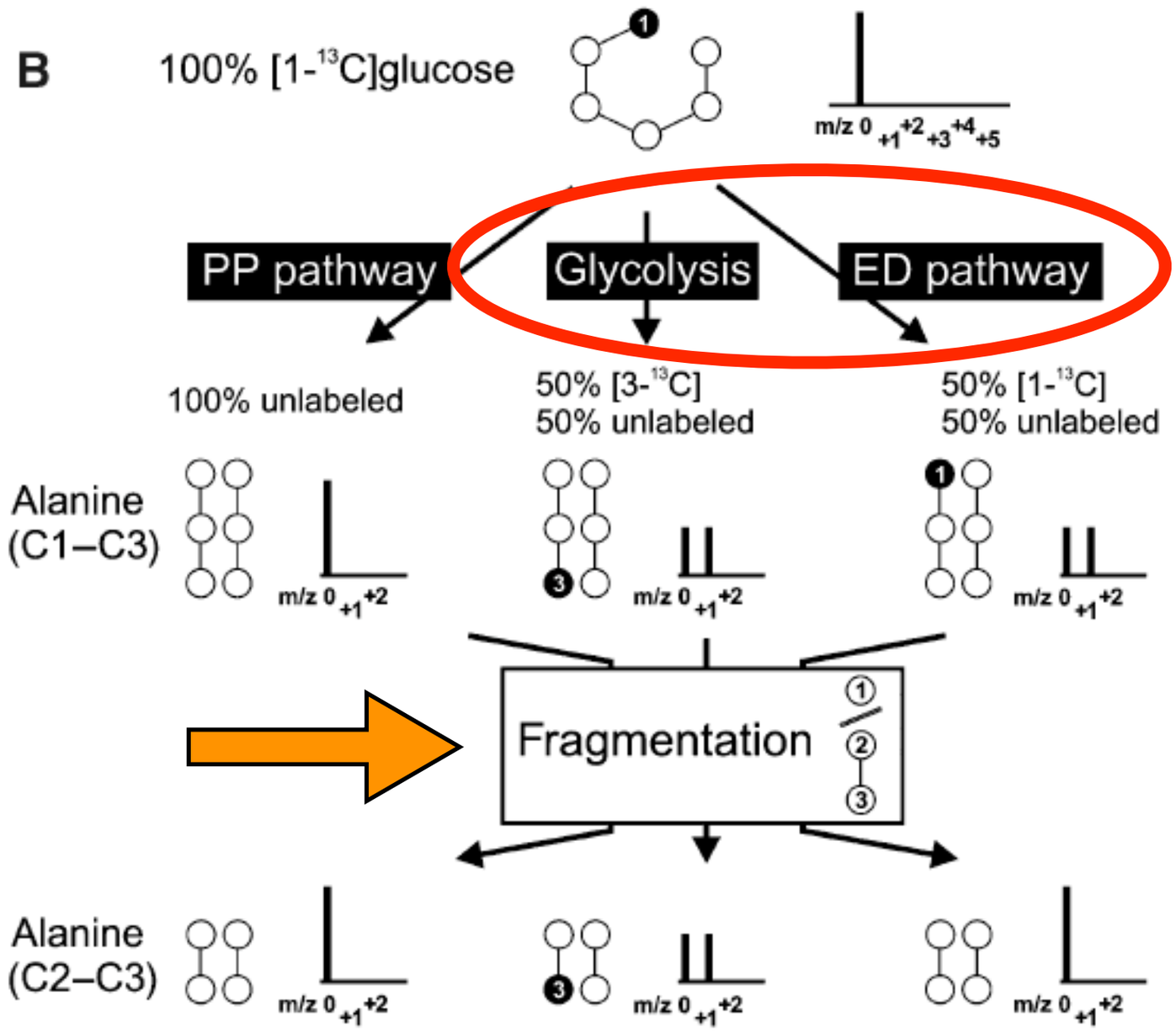
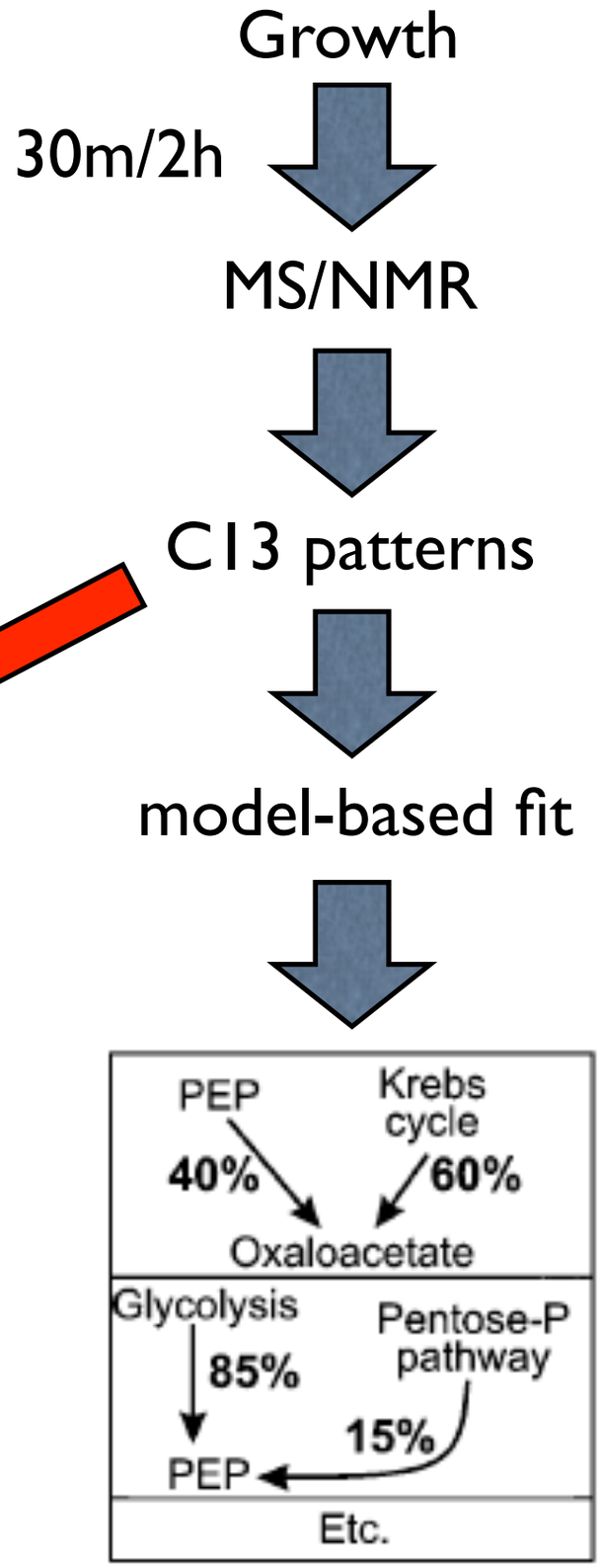
Problems

Purine Biosynthesis
AMP
GMP
ATP
ADP
Adenosine
dATP
dADP
Adenine
GTP
GDP
Guanosine
dGTP
dGDP
Guanine
Glucuronate Metabolism
Vitamin C
Glucuronate
Pentose Interconversions
Histidine
Histidine Metabolism
Serine
Methionine
Cysteine
Aspartate Amino Acid Group Synthesis
Tryptophan
Threonine
Asparagine
Other Sugar Metabolism
Aromatic Amino Acid Synthesis
Ribulose-5P
Aspartate
Lysine
Inositol
Lactose
Galactose
Fructose
Tyrosine
Porphyrins and Corrinoids Metabolism
Inositol Metabolism
Pentose Phosphate Pathway
Fumarate
Succinate
Haemaglobin
Vitamin B12
Cytochromes
Chlorophyll
Aerobic Sugar Respiration
Oxaloacetate
Citric acid cycle
Sucrose
Cellulose
Glucose-1P
Glucose-6P
Fructose-6P
GAD-3P
Pyruvate
Acetyl-CoA
2-oxo glutarate
Cellulose and Sucrose Metabolism
Anaerobic Sugar Respiration
Glycolysis and Gluconeogenesis
Pyruvate Decarbox.
Glucose
Pyruvate Metabolism
Amylose
Glycogen
Glutamine
Glutamate Amino Acid Group Synthesis
Glucosamine
Chitin
Lactate
Ethanol
Starch and Glycogen Metabolism
Amino Sugars Metabolism
Fats
Glycine
Serine
Alanine
Glutamate
Proline
Small Amino Acid Synthesis
Fatty Acid Metabolism
Urea Cycle
Pyrimidine Synthesis
Valine
Threonine
Leucine
Iso-leucine
Fatty Acid
Urea
Arginine
Aspartate
Uridine
Cytidine
Uracil
UTP
Thymine
dTTP
Cytosine
CTP
CDP
dCTP
Branched Amino Acid Synthesis

1. Experimental details *[Sauer, Molec. Sys. Biol. 06]*
2. Timescales (chemical vs genetic vs cellular vs experimental ...)
3. Stationary state?



?



	G6P	F6P	FDP	DHAP	GA3P	13DPG	3PG	2PG	PEP	GL6P	GO6P	RU5P	R5P	Xu5P	S7P	E4P	PRPP	IMP	R1P	AMP	GLC	23DPG	PYR	LAC	HX	ADE	ADO	INO	ADP	ATP	NAD	NADH	NADP	NADPH
HK	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	1	-1	0	0	0	0
PGI	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PFK	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0
ALD	0	0	-1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TPI	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GAPDH	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0
PGK	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0
DPGM	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
DPGase	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0
PGM	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EN	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PK	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	-1	1	0	0	0	0
LDH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	1	-1	0	0
G6PDH	-1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1
PGL	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GL6PDH	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1
RPI	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
XPI	0	0	0	0	0	0	0	0	0	0	0	-1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TKI	0	0	0	0	1	0	0	0	0	0	0	0	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TKII	0	1	0	0	1	0	0	0	0	0	0	0	0	-1	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TA	0	1	0	0	-1	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AMPase	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
ADA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0
AK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	-1	0	1	-1	0	0	0	0
ApKR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	2	-1	0	0	0
AMPDA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AdPRT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	1	0	0	0	0	0	0	-1	0	0	0	0	0	0	0
IMPase	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
PNPase	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	-1	0	0	0	0	0	0
PRM	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PRPPsyn	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	-1	0	0	0
HGPRT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0
GLCin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
23DPGout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0
PYRout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0
LACout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0
Hxout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0
ADEin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
ADOin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
INOin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
ADPin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
ATPout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0
NADin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
NADHout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0
NADPin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
NADPHout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1

	G6P	F6P	FDP	DHAP	GA3P	13DPG	3PG	2PG	PEP	GL6P	GO6P	RU5P	R5P	Xu5P	S7P	E4P	PRPP	IMP	R1P	AMP	GLC	23DPG	PYR	LAC	HX	ADE	ADO	INO	ADP	ATP	NAD	NADH	NADP	NADPH
HK	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	1	-1	0	0	0	0
PGI	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PFK	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	-1	0	0	0	0
ALD	0	0	-1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TPI	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GAPDH	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0
PGK	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0
DPGM	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
DPGase	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0
PGM	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
EN	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PK	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	-1	1	0	0	0	0
LDH	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	1	-1	0	0
G6PDH	-1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1
PGL	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
GL6PDH	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1
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TKI	0	0	0	0	1	0	0	0	0	0	0	0	-1	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TKII	0	1	0	0	1	0	0	0	0	0	0	0	0	-1	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TA	0	1	0	0	-1	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AMPase	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	1	0	0	0	0	0	0	0
ADA	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0
AK	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	-1	0	1	-1	0	0	0	0
ApKR	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	2	-1	0	0	0	0
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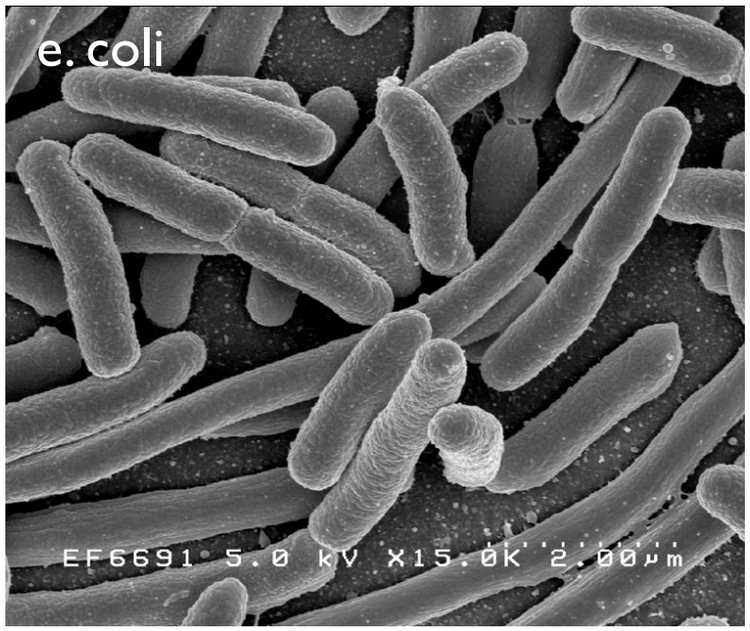
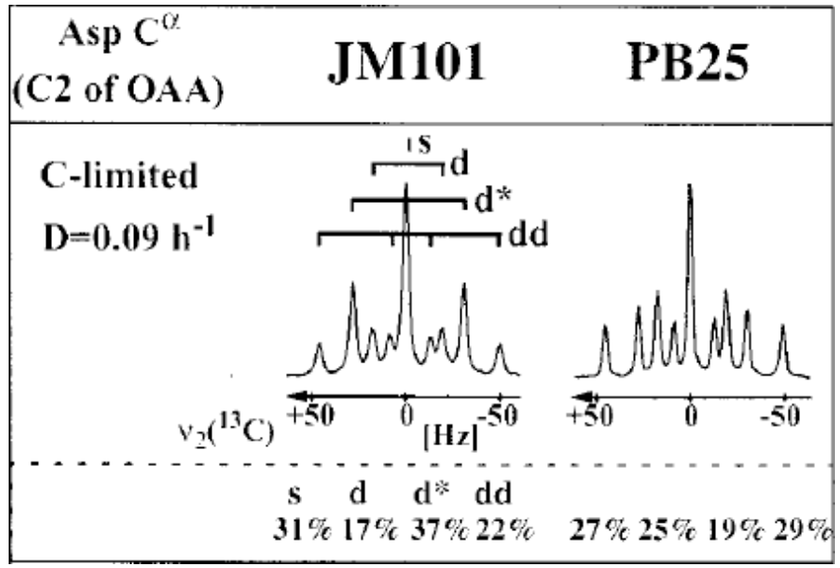
AdPRT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	1	0	0	0	0	0	0	-1	0	0	0	0	0	0	0
IMPase	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
PNPase	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	1	0	0	-1	0	0	0	0	0	0
PRM	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PRPPsyn	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	1	0	0	1	0	0	0	0	0	0	0	0	0	-1	0	0	0	0
HGPRT	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	1	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0
GLCin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
23DPGout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0	0
PYRout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0	0
LACout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0	0
Hxout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0	0	0	0	0	0
ADEin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0
ADOin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
INOin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
ADPin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
ATPout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0	0	0
NADin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0
NADHout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1	0	0
NADPin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0
NADPHout	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	-1

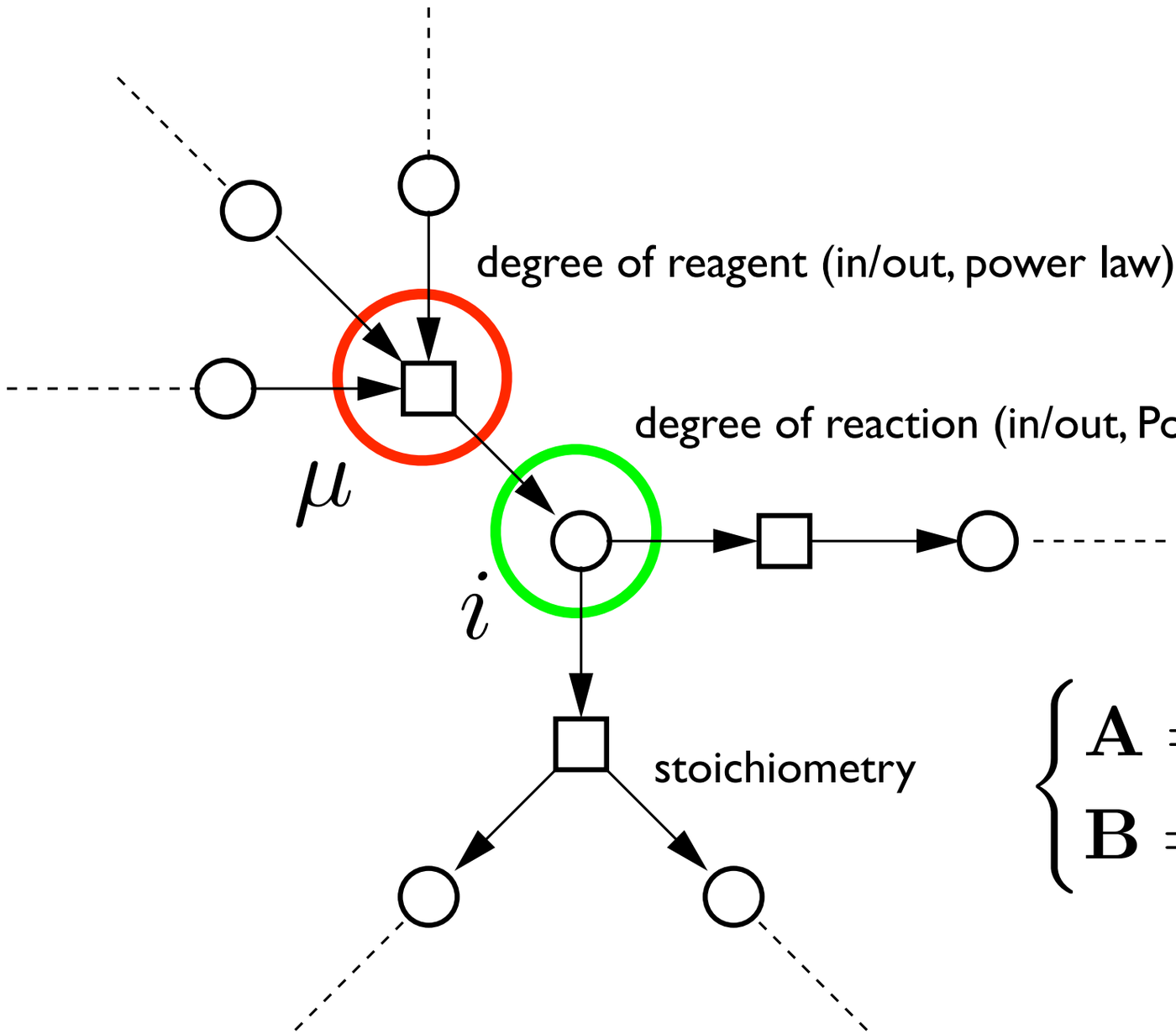
?

fluxes





bipartite graph



$$\begin{cases} \mathbf{A} = \{a_i^\mu\} & \text{output} \\ \mathbf{B} = \{b_i^\mu\} & \text{input} \end{cases}$$

N reactions (balls), P reagents (squares)

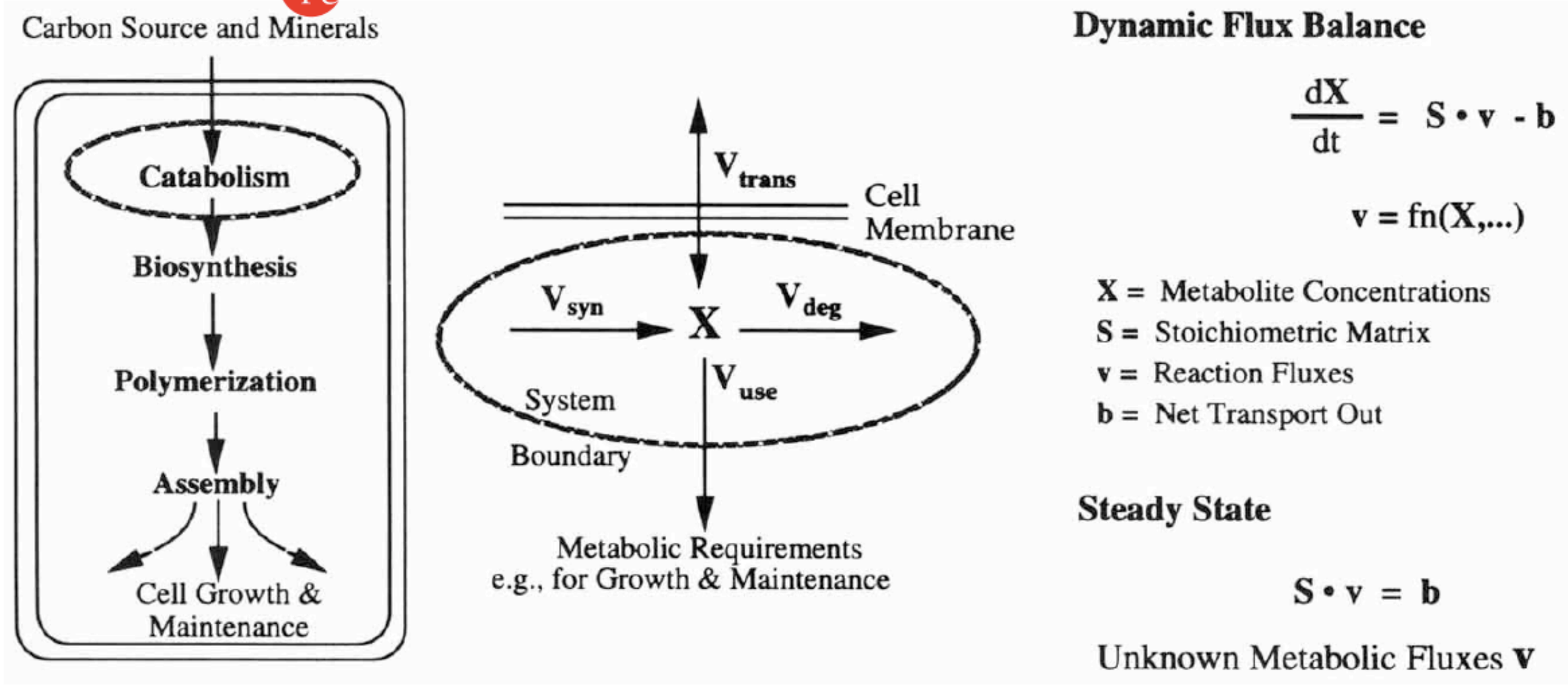
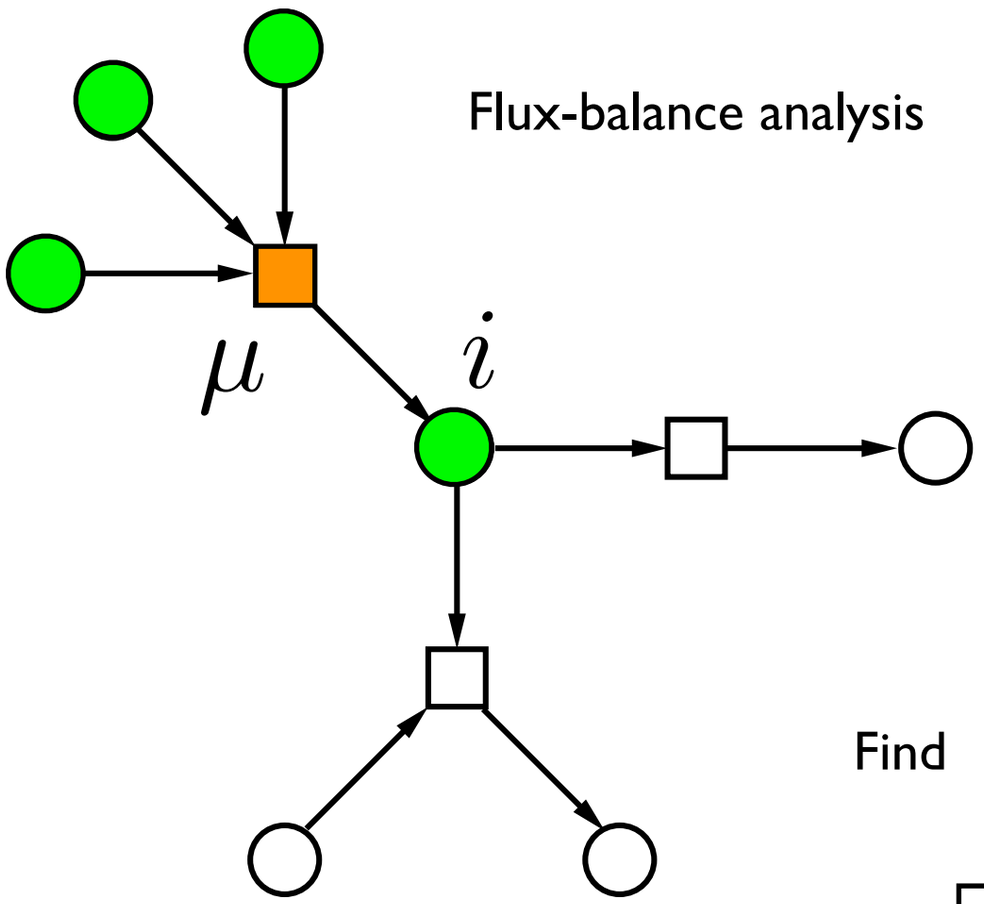


FIGURE 1. Flux balance models use material balances around each metabolite in a metabolic network. Inputs to the metabolic network include the carbon source provided in the culture medium while the outputs include by-products, additional biomass generated as well as the maintenance requirements.

Metabolic Flux Balancing: Basic Concepts, Scientific and Practical Use

Amit Varma[1] and Bernhard O. Palsson*



Flux-balance analysis

$\boldsymbol{S}$ stoichiometric matrix (P by N)

$\mathbf{u} = \{u^{\mu}\}_{\mu=1}^{P}$ net cellular uptake

$\boldsymbol{\nu} = \{\nu_i\}_{i=1}^{N}$ flux vector

Find $\boldsymbol{\nu} = \{0 \leq \nu_i \leq \nu_{max}\}_{i=1}^{N}$ s.t.

$$\boxed{\mathbf{S}\ \boldsymbol{\nu} = \mathbf{u}}$$ (mass balance)

MC sampling unfeasible (E. coli)

+ maximization of biomass yield
+ maximization of ATP yield
+ minimization of total flux
+ minimization of glc consumption
+ ...

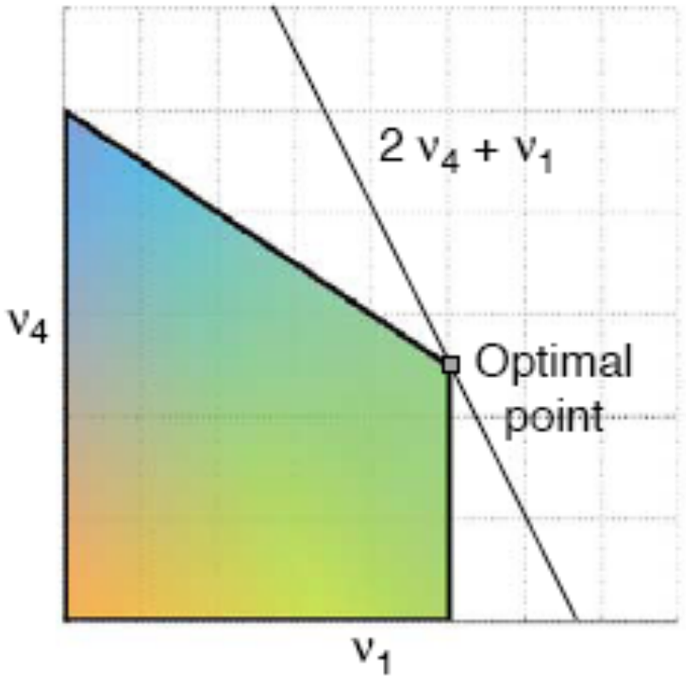
Molecular Systems Biology 3; Article number 119; doi:10.1038/msb4100162
Citation: *Molecular Systems Biology* **3:119**

www.molecularsystemsbiology.com

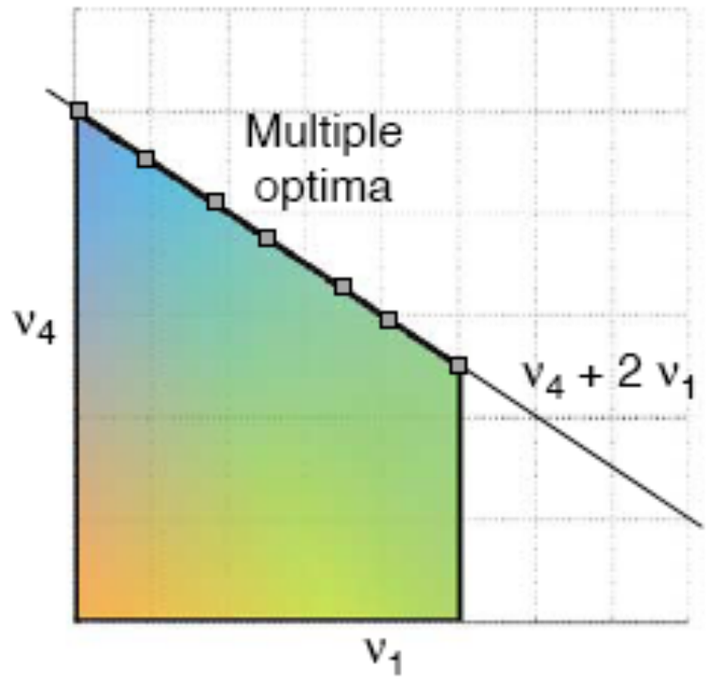
molecular systems biology

Systematic evaluation of objective functions for predicting intracellular fluxes in *Escherichia coli*

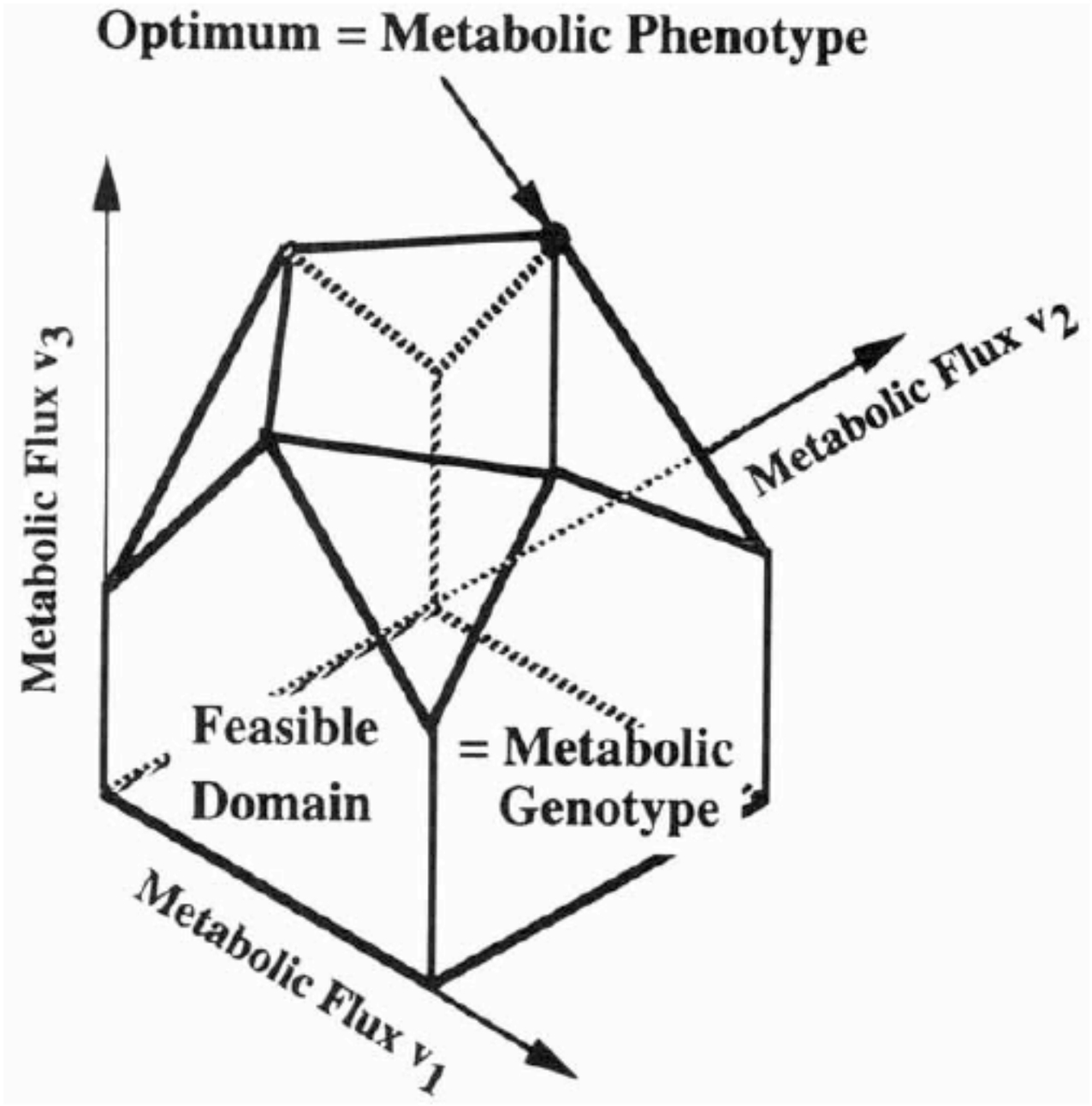
Robert Schuetz[1,2,3], Lars Kuepfer[1,3,4] and Uwe Sauer[1,2,*]



Objective (Z) = $2v_4 + v_1$

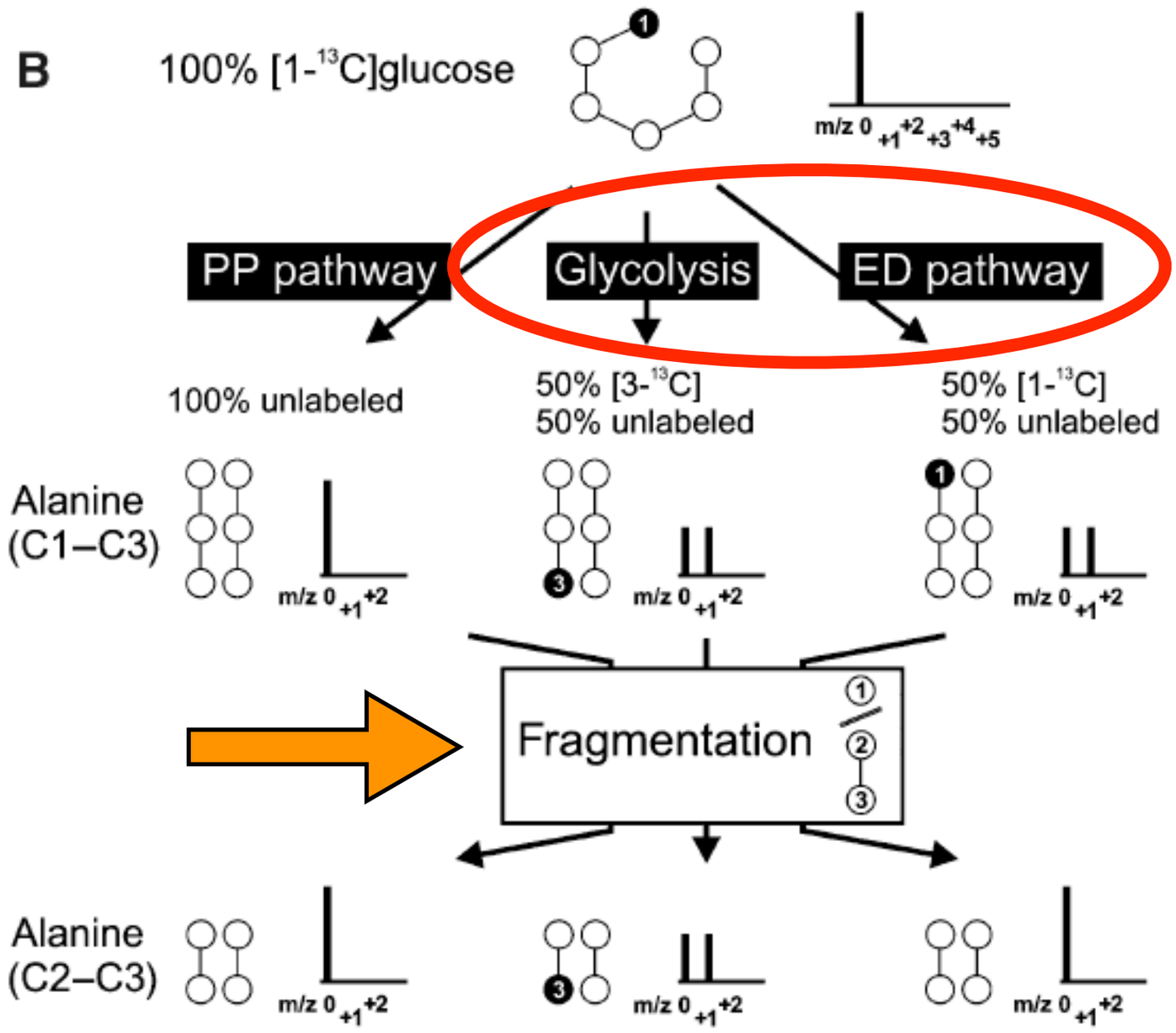


Objective (Z) = $v_4 + 2v_1$



Max biomass	$\max \frac{\nu_{\mathrm{biomass}}}{\nu_{\mathrm{glc}}}$	Evolution drives selection towards maximal biomass yield
Max ATP	$\max \frac{\nu_{\mathrm{ATP}}}{\nu_{\mathrm{glc}}}$	Evolution drives selection towards maximal energetic efficiency
Min total flux	$\min \sum_{i=1}^{N} \nu_i^2$	Evolution drives selection towards maximal enzymatic efficiency
Min glc consumption	$\min \frac{\nu_{\mathrm{glc}}}{\nu_0}$	Evolution drives selection towards optimal usage of substrate

1. Experimental details *[Sauer, Molec. Sys. Biol. 06]*
2. Timescales (chemical vs genetic vs cellular vs experimental ...)
3. Stationary state?



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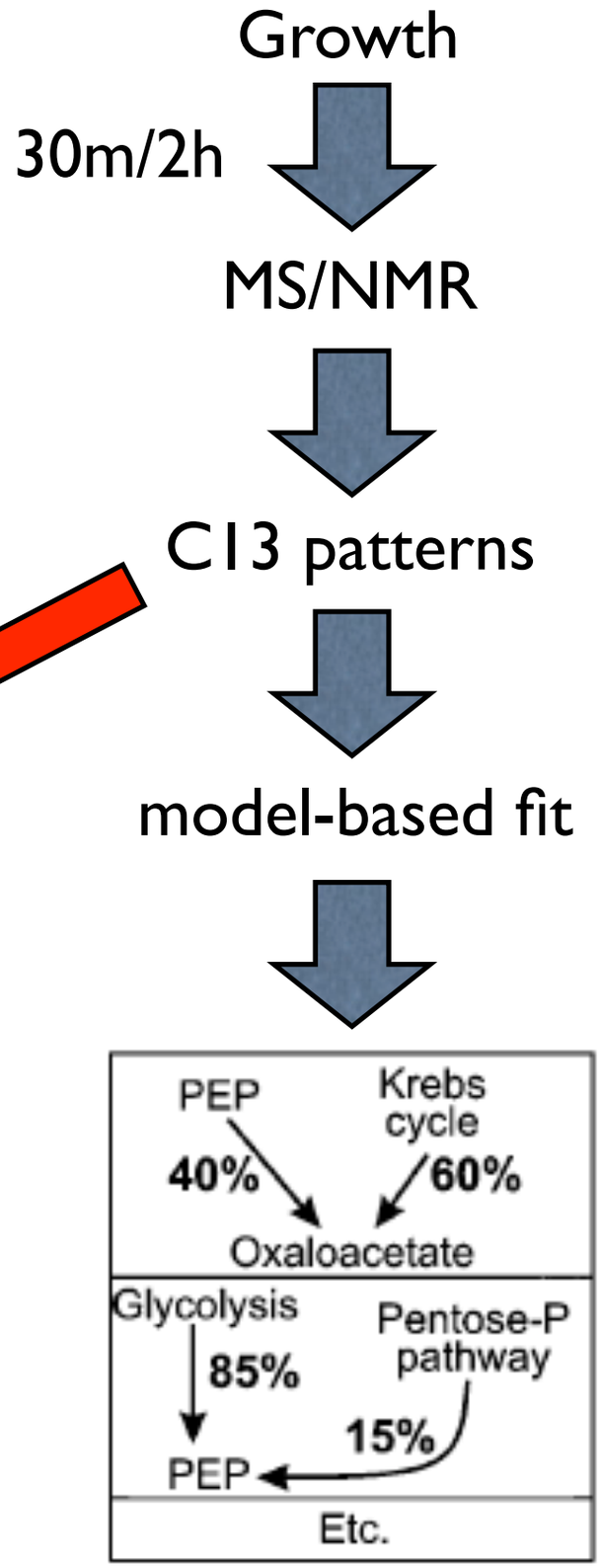

1. Experimental details *[Sauer, Molec. Sys. Biol. 06]*
2. Timescales (chemical vs genetic vs cellular vs experimental ...)
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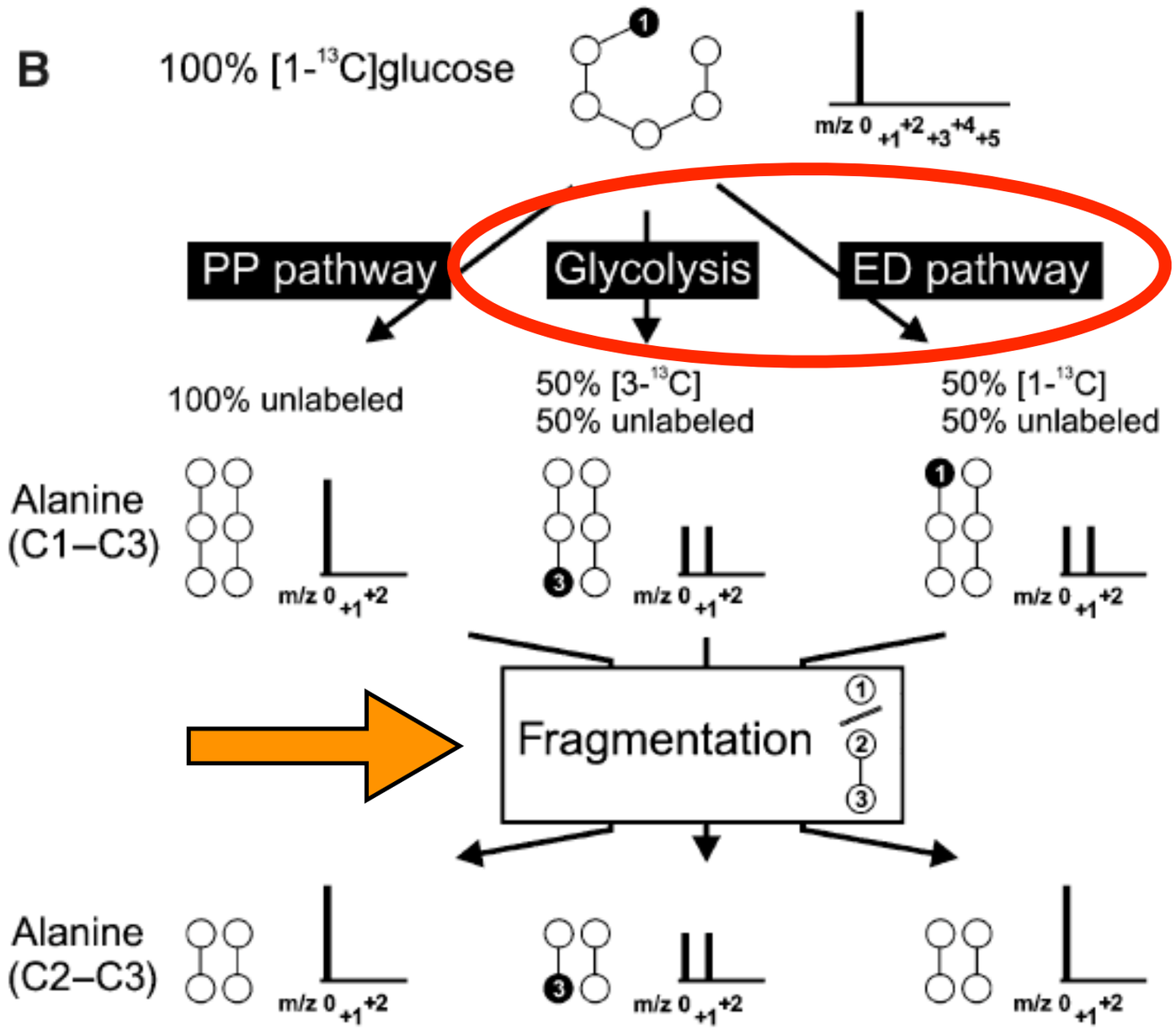

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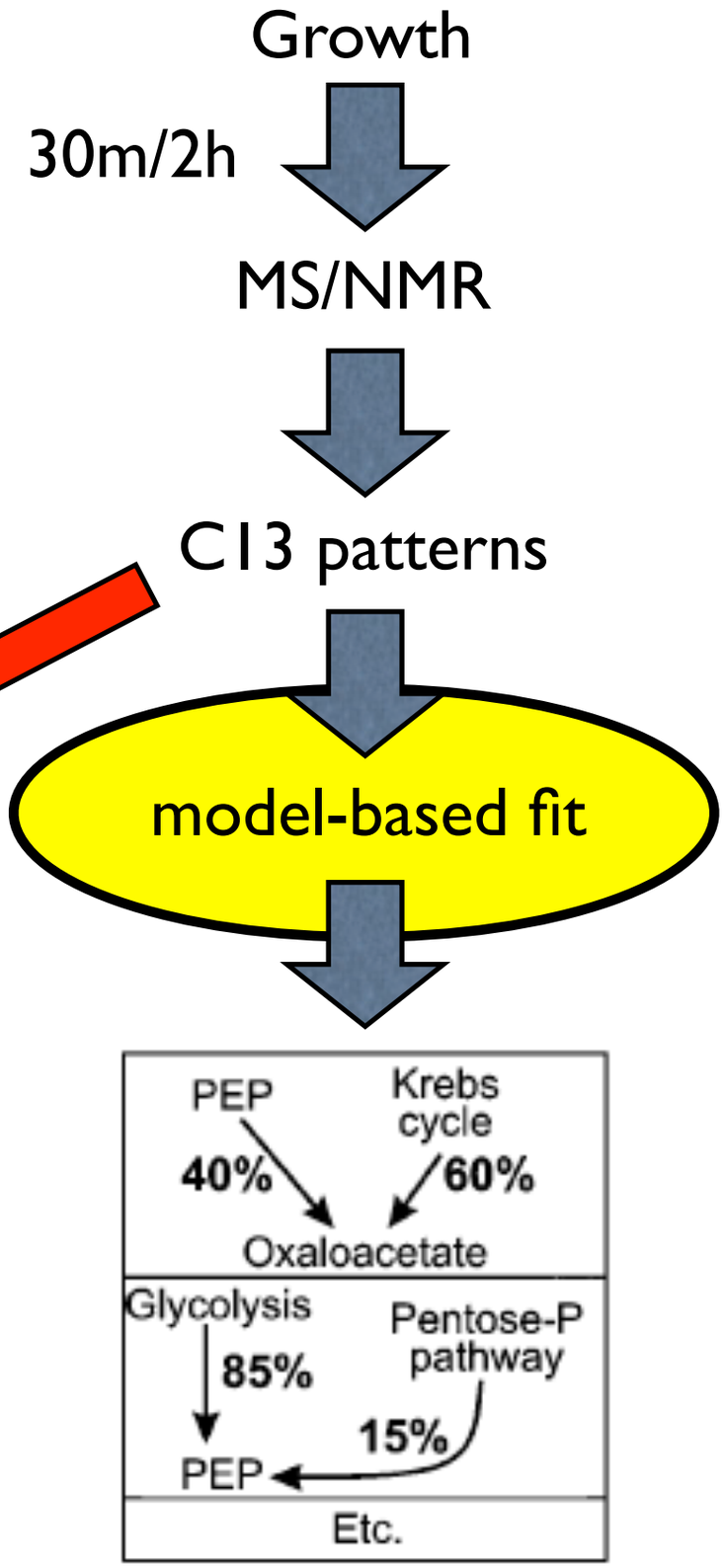
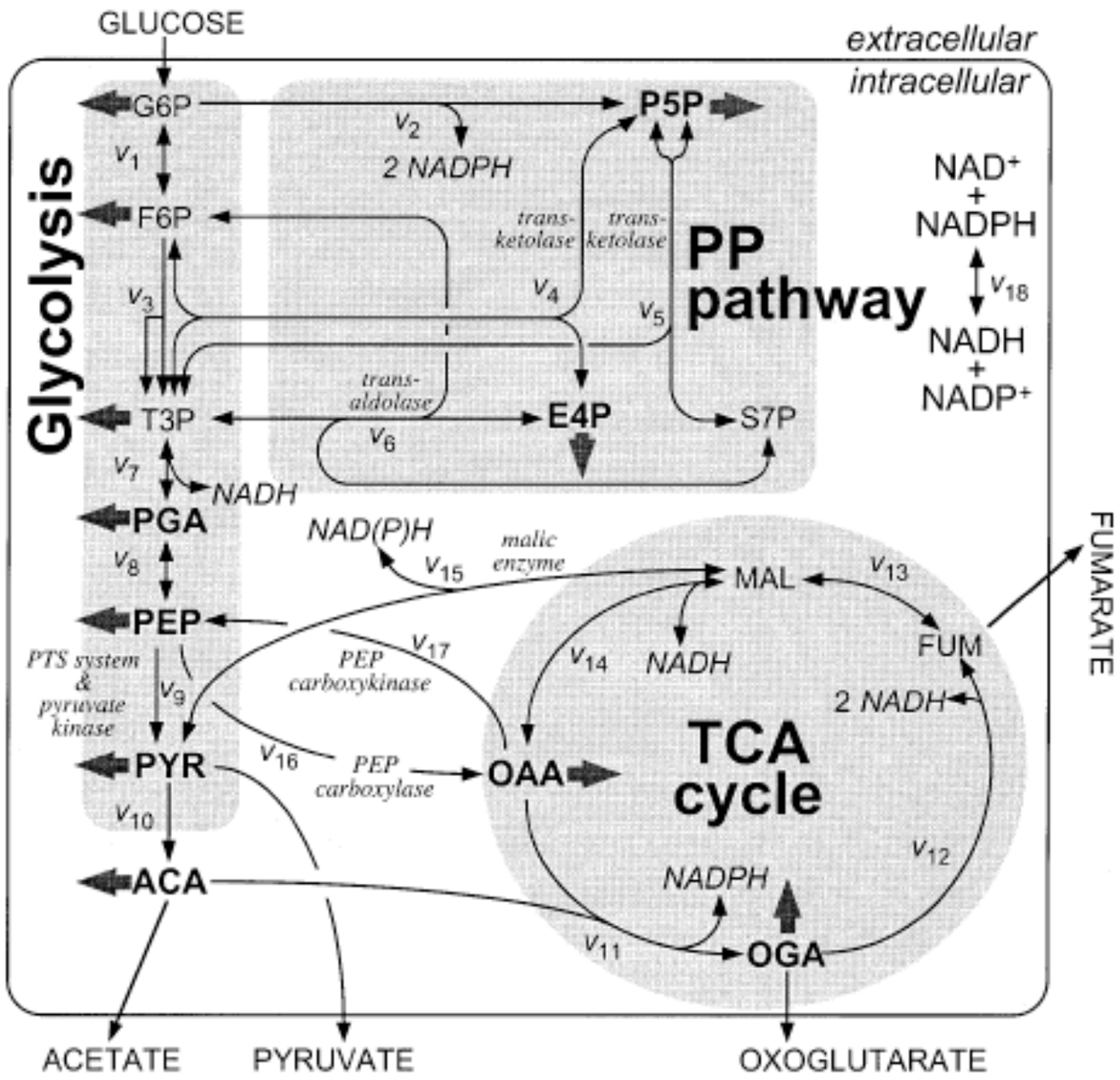


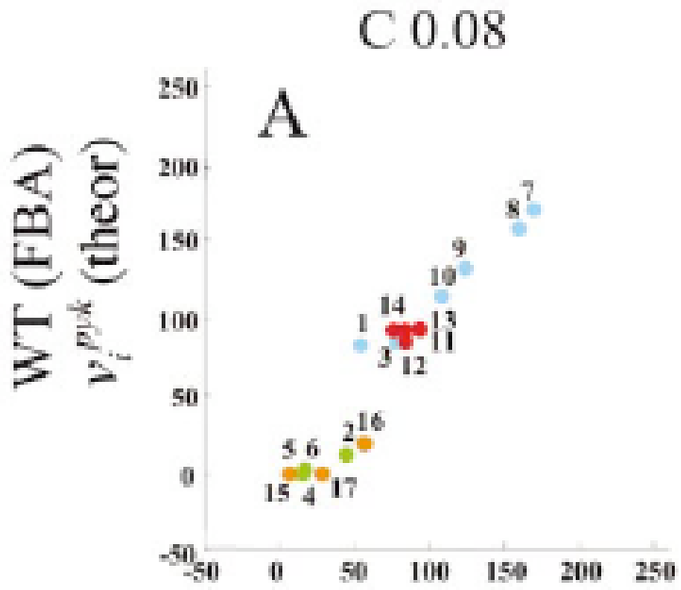
Analysis of optimality in natural and perturbed metabolic networks

*[PNAS **99** 15112 (2002)]*

Daniel Segrè, Dennis Vitkup, and George M. Church*

Lipper Center for Computational Genetics and Department of Genetics, Harvard Medical School, Boston, MA 02115





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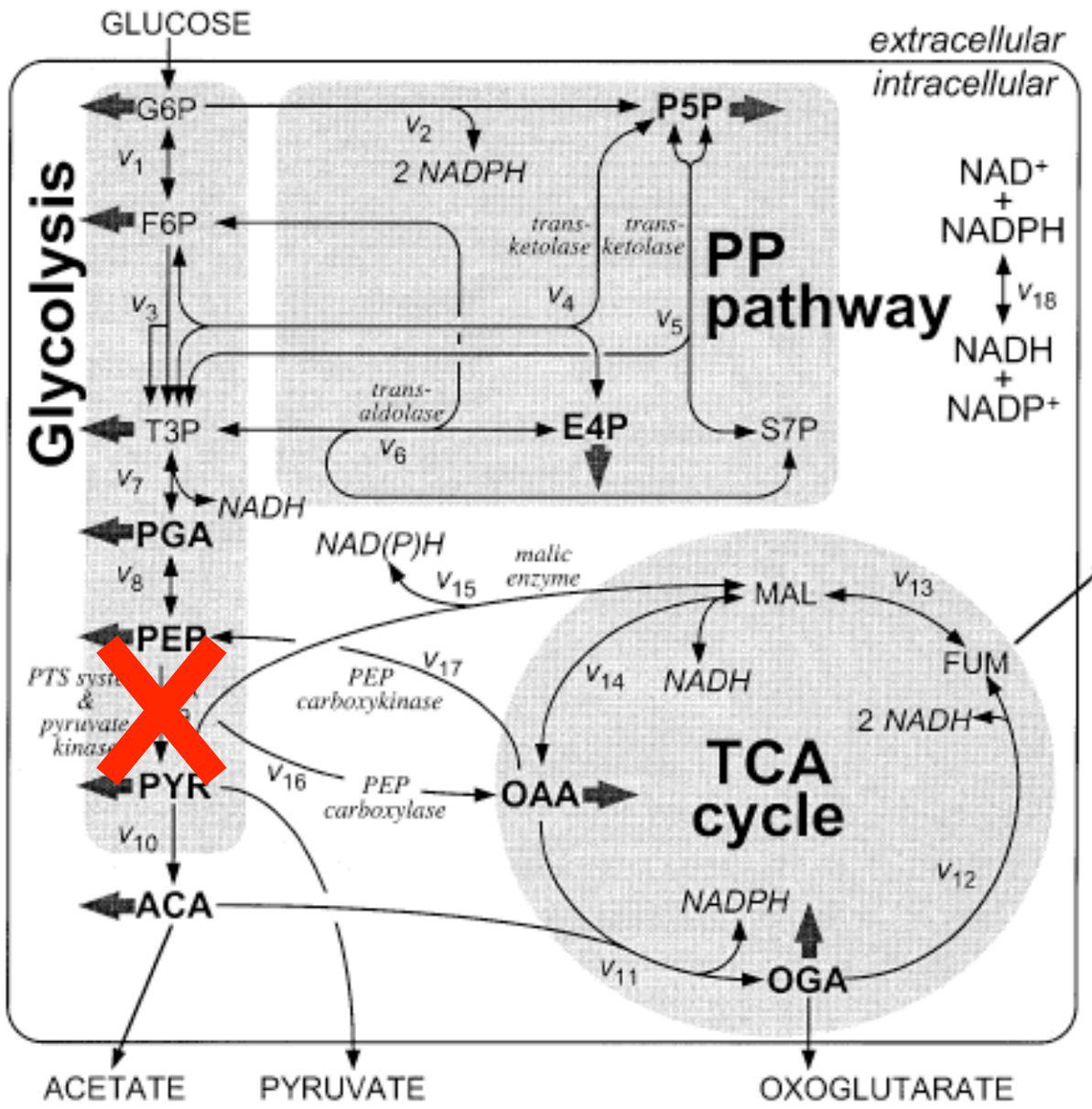
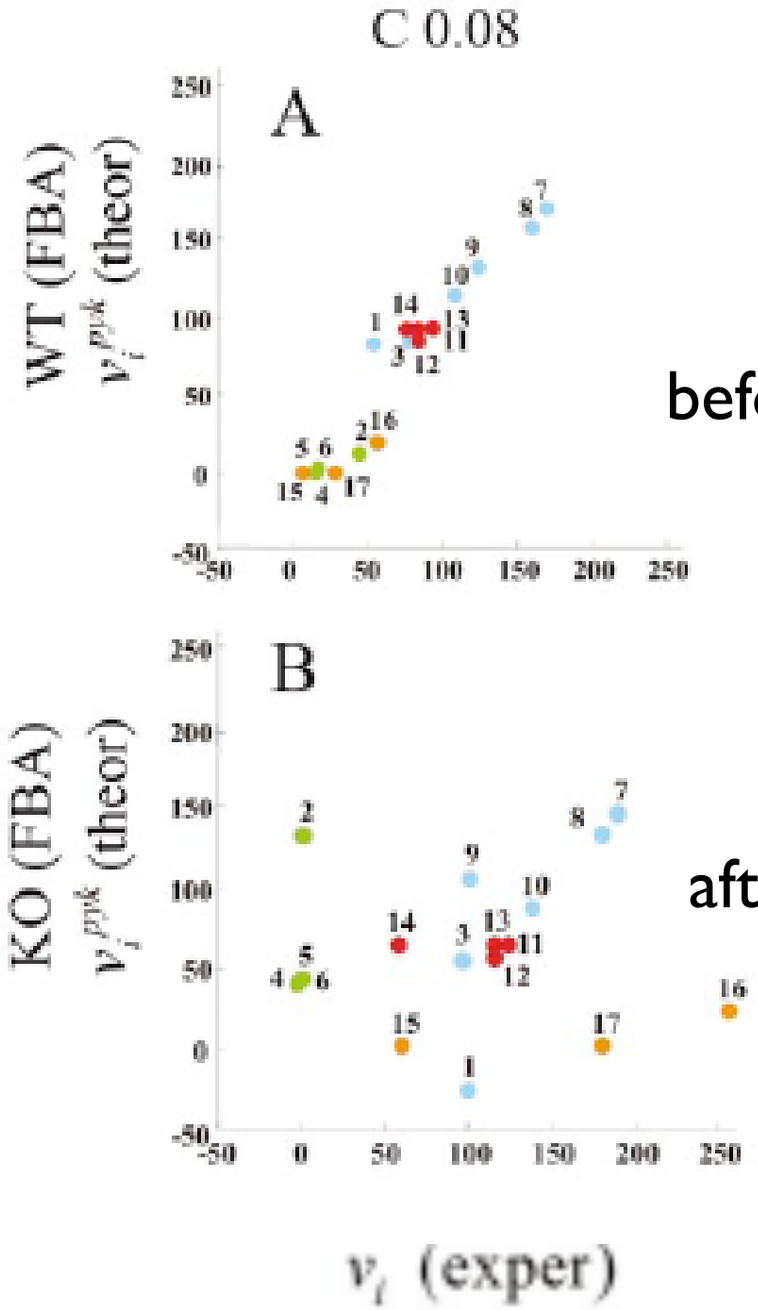




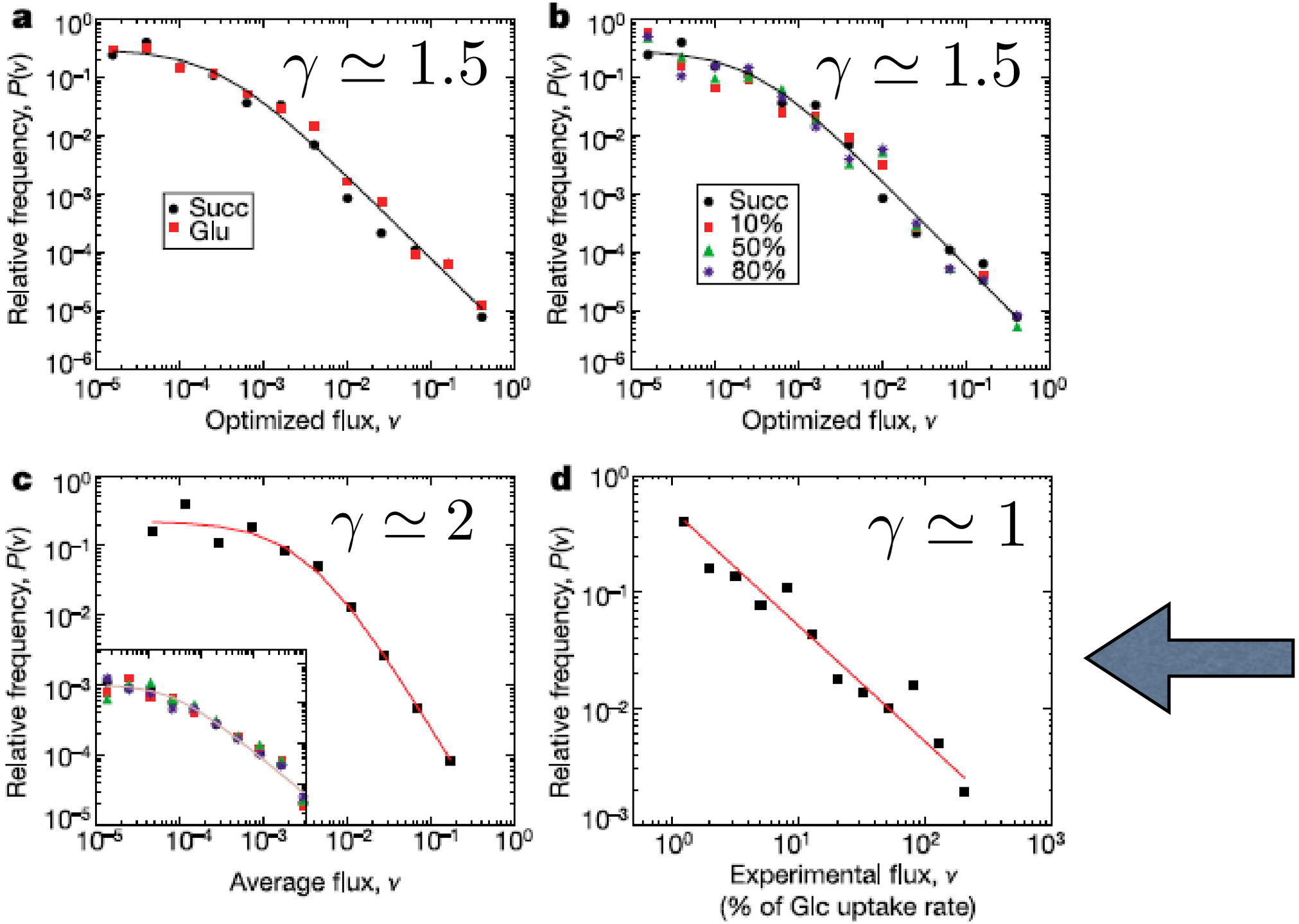
before KO

after KO

Global organization of metabolic fluxes in the bacterium *Escherichia coli*

E. Almaas[1], B. Kovács[1,2], T. Vicsek[2], Z. N. Oltvai[3] & A.-L. Barabási[1]

NATURE | VOL 427 | 26 FEBRUARY 2004 | www.nature.com/nature

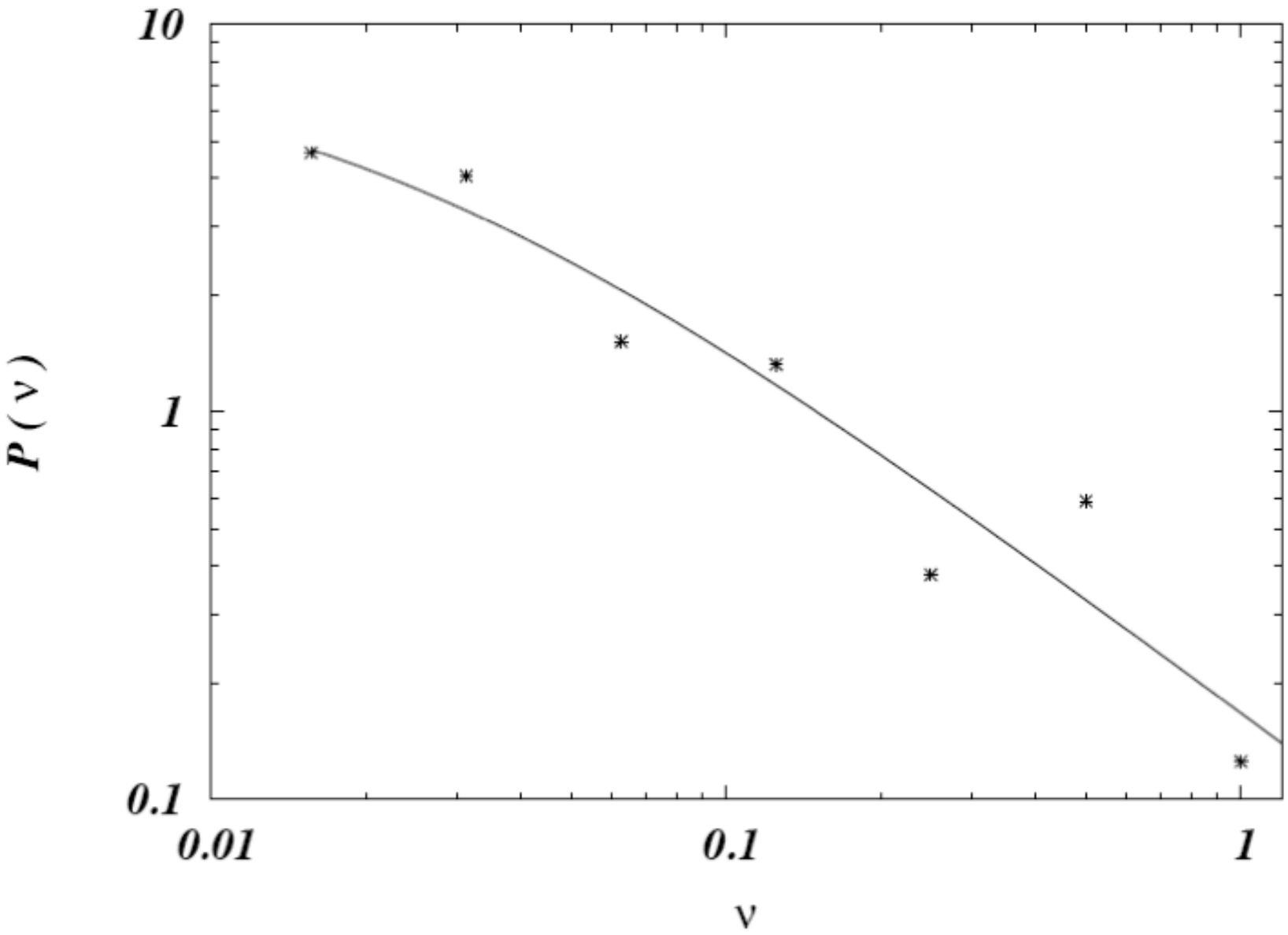


Estimating the size of the solution space of metabolic networks

[Braunstein et al, BMC Bioinfo. 08]

Alfredo Braunstein[1,2], Roberto Mulet[2], Andrea Pagnani[3]

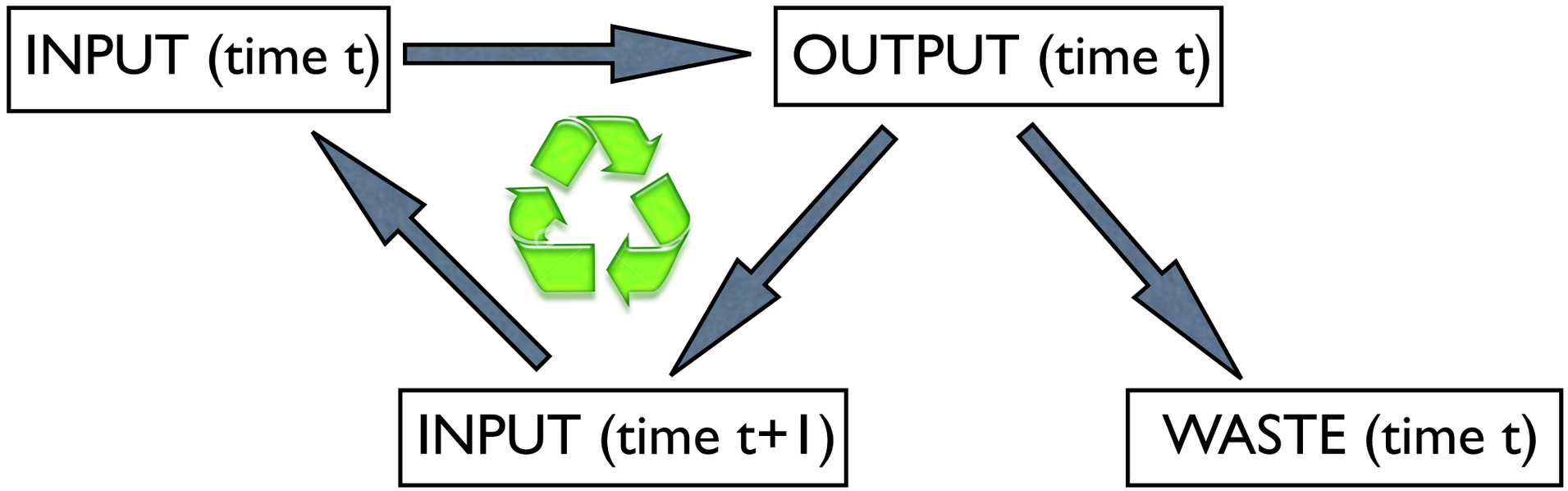
1.4 Figure 1.4 - Distribution of average fluxes



Distribution of average fluxes ($\bar{\nu}$) of the reactions for the E-Coli metabolism. $N = 1005$ and $M = 506$.

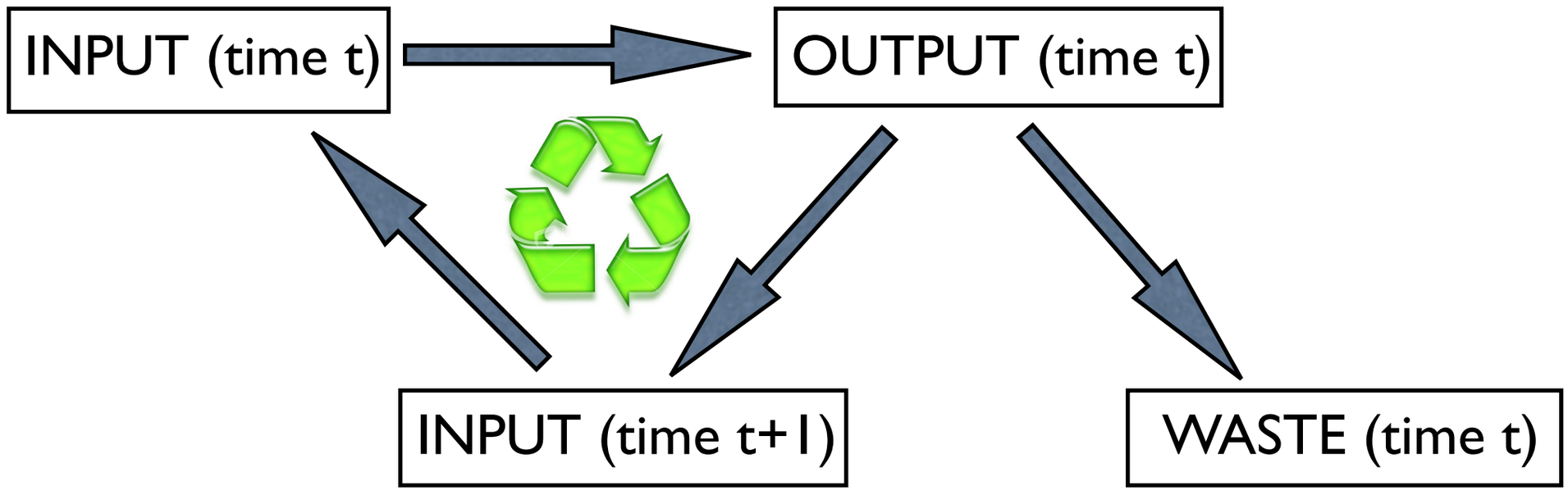
$$I^{\mu}(t) = \sum_{i \in \mu} b_i^{\mu} S_i(t)$$

$$O^{\mu}(t) = \sum_{i \in \mu} a_i^{\mu} S_i(t)$$



$$I^{\mu}(t+1) = O^{\mu}(t) - C^{\mu}(t) \qquad\qquad C^{\mu}(t) \geq 0$$

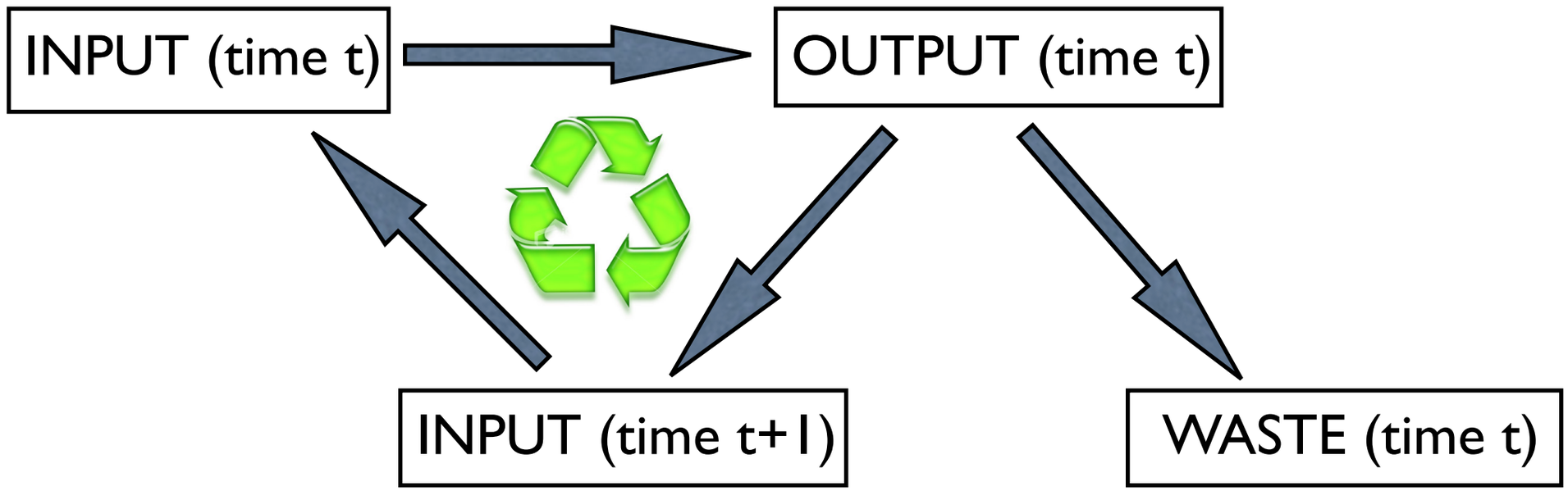
$$I^\mu(t) = \sum_{i \in \mu} b_i^\mu S_i(t) \qquad O^\mu(t) = \sum_{i \in \mu} a_i^\mu S_i(t)$$



$$I^\mu(t+1) = O^\mu(t) - C^\mu(t) \qquad C^\mu(t) \geq 0$$

Problem : which $\{\mathbf{S}(t)\}_{t \geq 0}$ are optimal?

$$I^\mu(t) = \sum_{i \in \mu} b_i^\mu S_i(t) \qquad O^\mu(t) = \sum_{i \in \mu} a_i^\mu S_i(t)$$



$$I^\mu(t+1) = O^\mu(t) - C^\mu(t) \qquad C^\mu(t) \geq 0$$

Problem : which $\{\mathbf{S}(t)\}_{t \geq 0}$ are optimal?

Von Neumann's recipe : focus on paths such that $I^\mu(t+1) = \rho I^\mu(t)$

$$\left.\begin{aligned} C^\mu(t) &= c^\mu \rho^t \\ S_i(t) &= s_i \rho^t \end{aligned}\right\} \rightarrow \text{maximize } \rho$$

$$\mathbf{C}(t) = \mathbf{O}(t) - \rho\mathbf{I}(t) \geq 0 \quad \Rightarrow \quad \mathbf{c} = (\mathbf{A} - \rho\mathbf{B})\mathbf{s} \geq 0$$

constraints $\quad \mathbf{c} = \{c^\mu \geq 0\}_{i=1}^{P}$

variables $\quad \mathbf{s} = \{s_i \geq 0\}_{i=1}^{N}$

Optimal metabolic networks :

$$\text{maximize } \rho \text{ subject to} \quad c^\mu \equiv \sum_{i \in \mu} s_i (a_i^\mu - \rho b_i^\mu) \geq 0 \quad \forall \mu$$

1) compute $\rho^\star$; 2) look at $P(s)$ etc.

$$\mathbf{C}(t) = \mathbf{O}(t) - \rho\mathbf{I}(t) \geq 0 \quad \Rightarrow \quad \mathbf{c} = (\mathbf{A} - \rho\mathbf{B})\mathbf{s} \geq 0$$

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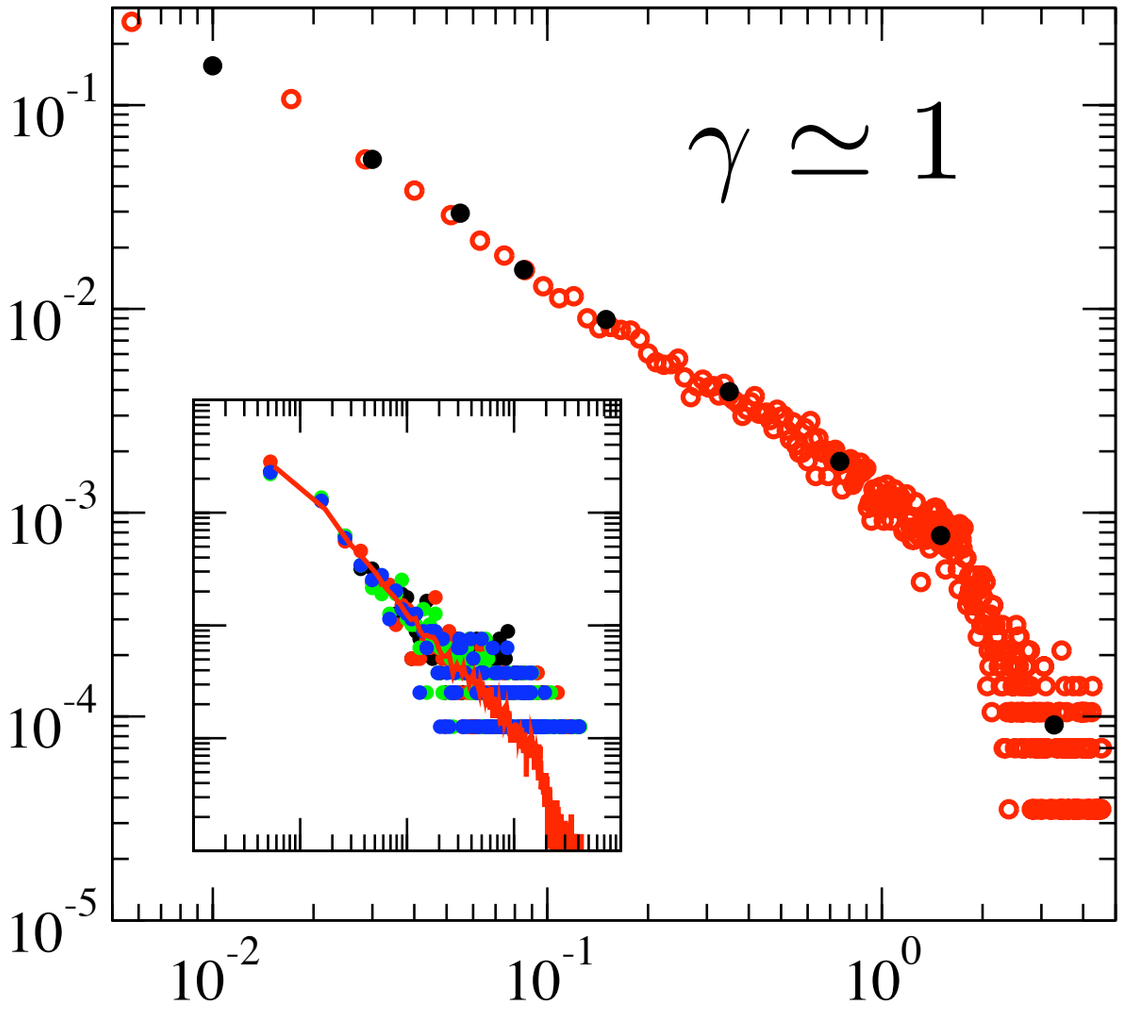
1) compute $\rho^\star$; 2) look at $P(s)$ etc.

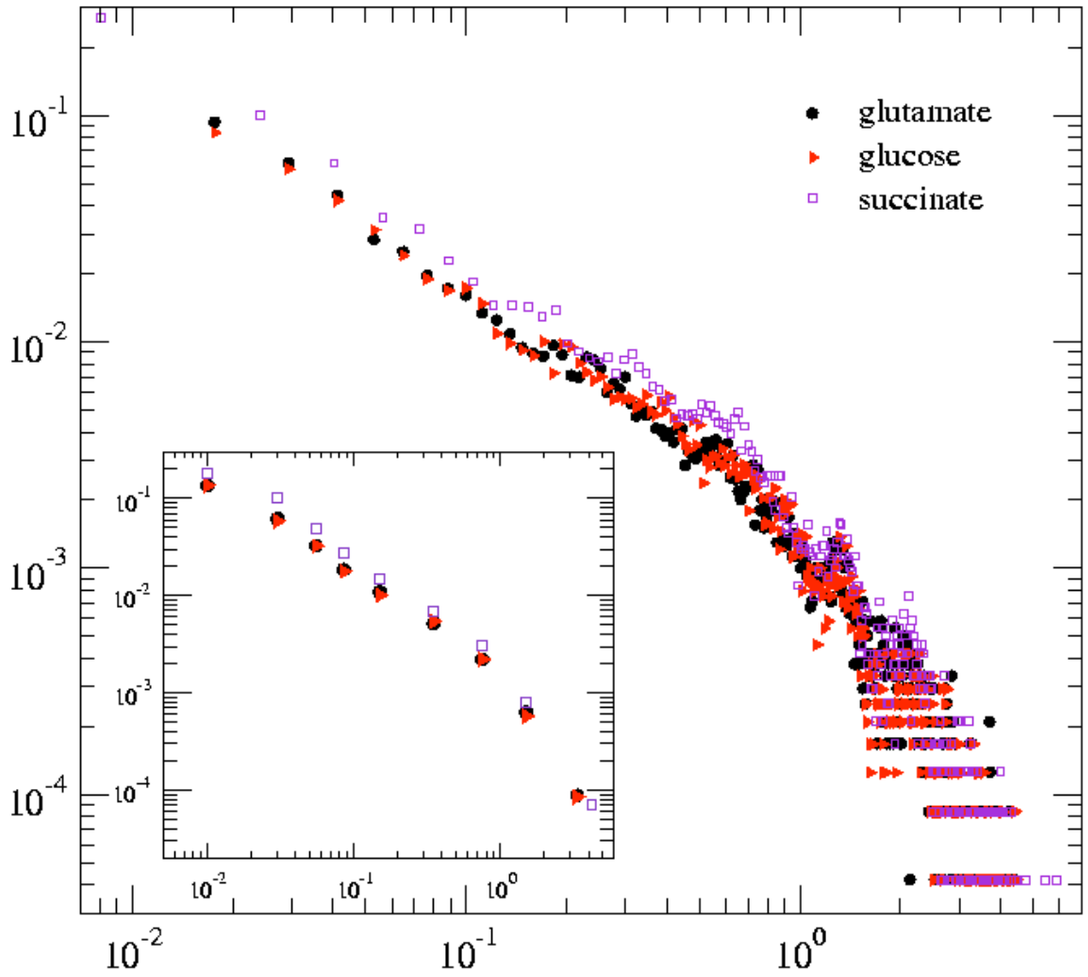
$$\begin{cases} \mathbf{FBA}: & (\mathbf{A} - \mathbf{B})\boldsymbol{\nu} = \mathbf{0} \\ \mathbf{VN}: & (\mathbf{A} - \rho\mathbf{B})\boldsymbol{s} \geq \mathbf{0} \end{cases}$$

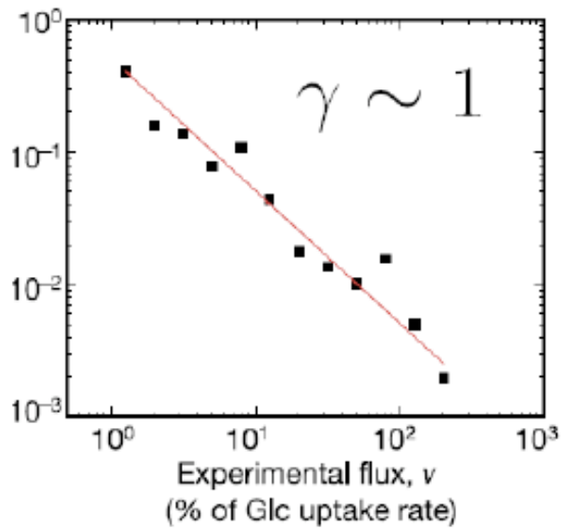
Note : FBA results recovered if $\begin{cases} \rho^\star = 1 & \text{and} \\ \mathbf{c} = \mathbf{0} \end{cases}$

e. coli : $\rho^\star = 1$

flux distributions

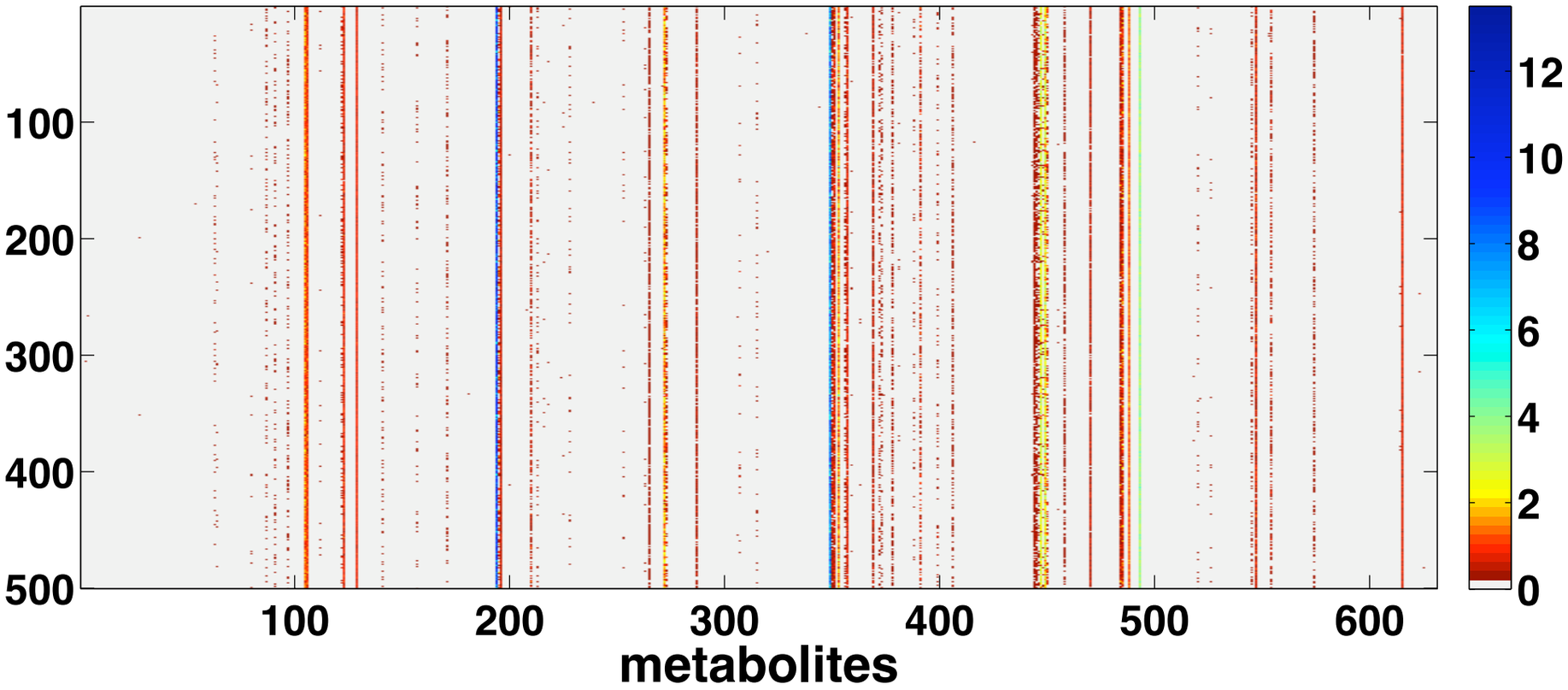




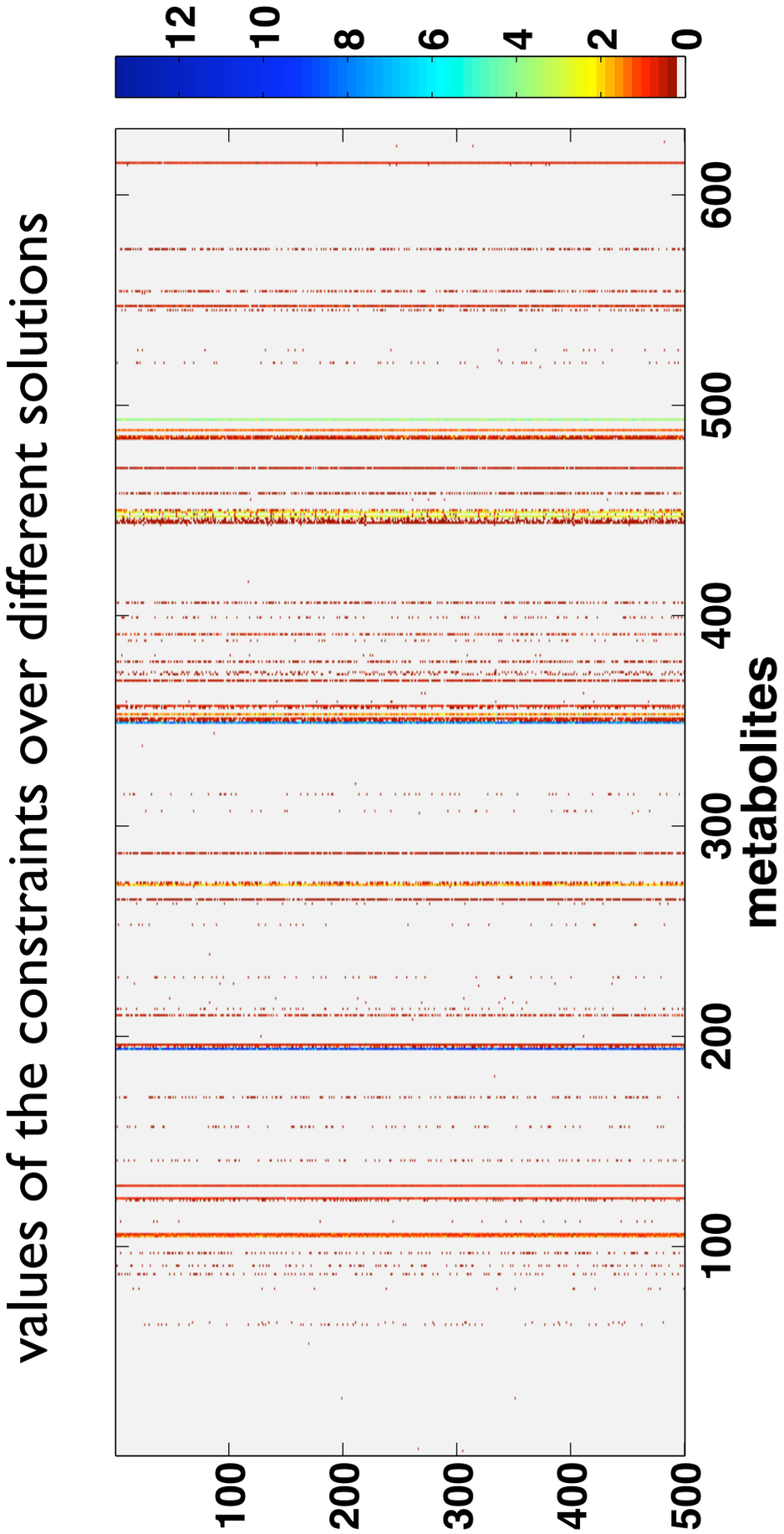


expts

values of the constraints over different solutions

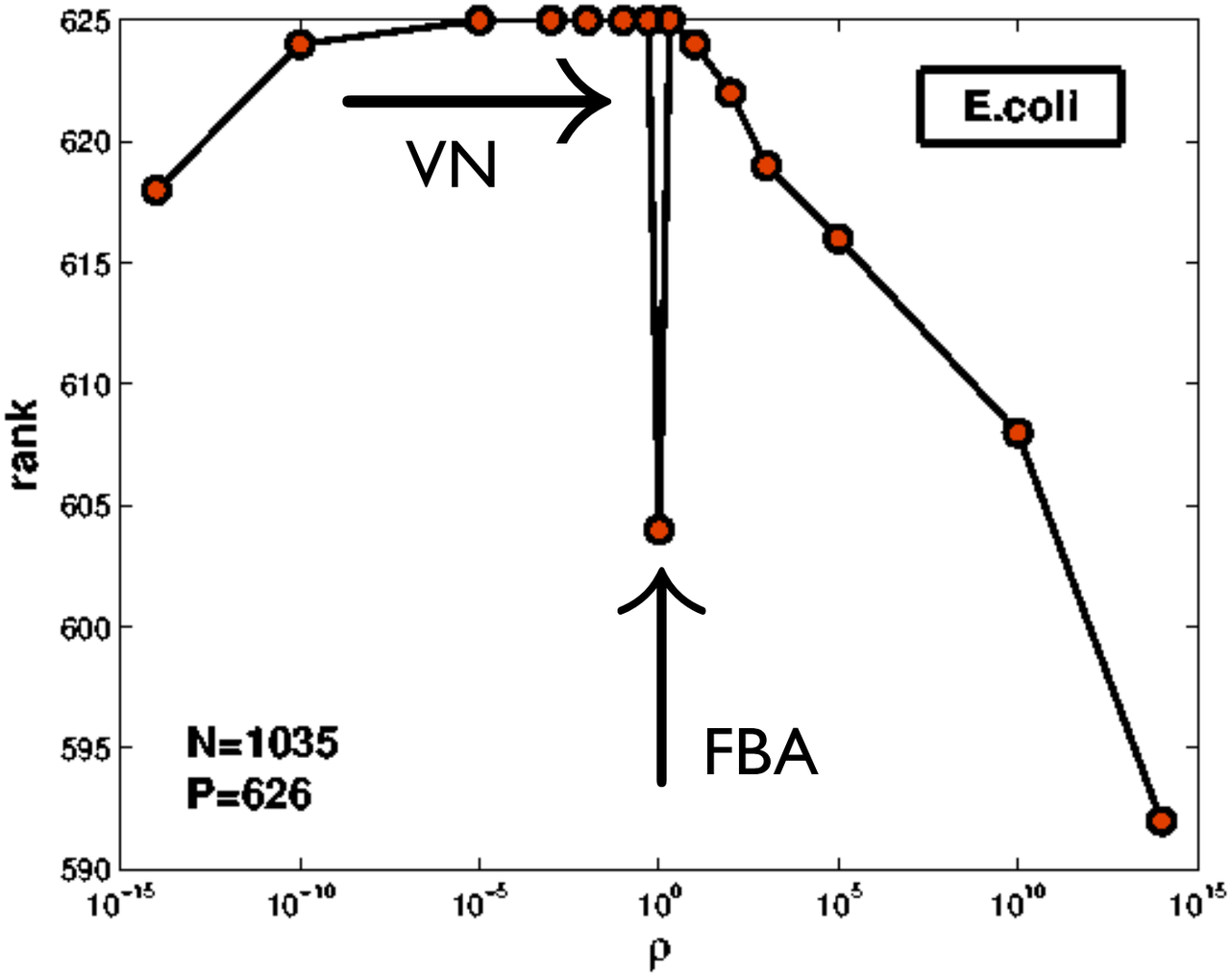


$$\begin{cases} \mathrm{FBA}: & (\mathbf{A}-\mathbf{B})\boldsymbol{\nu} = \mathbf{0} \\ \mathrm{VN}: & (\mathbf{A}-\rho\mathbf{B})\boldsymbol{s} \geq \mathbf{0} \end{cases}$$

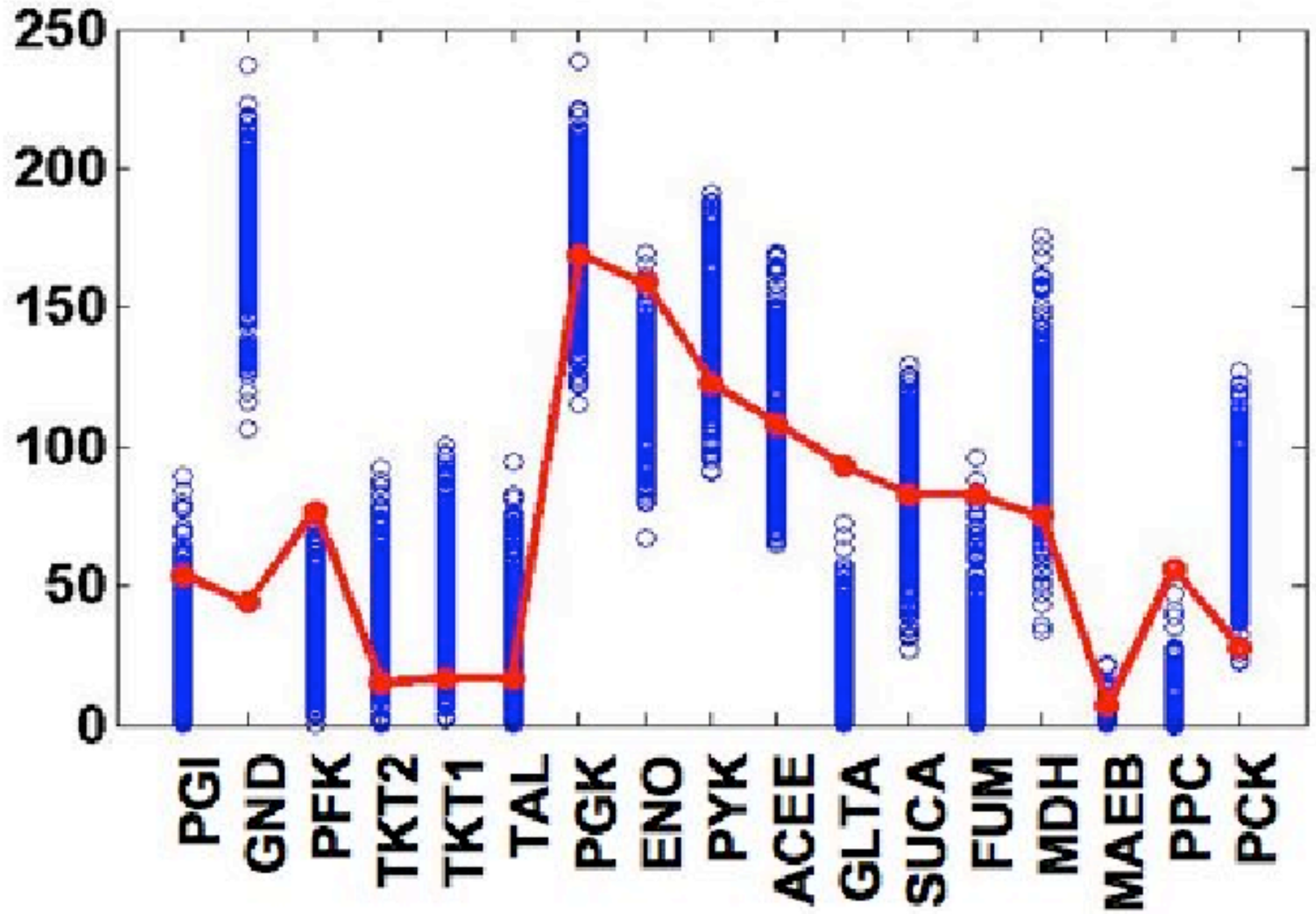


$$\begin{cases} \mathbf{FBA}: & (\mathbf{A}-\mathbf{B})\boldsymbol{\nu}=\mathbf{0} \\ \mathbf{VN}: & (\mathbf{A}-\rho\mathbf{B})\boldsymbol{s}\geq\mathbf{0} \end{cases}$$

$$\text{rank of } \ \boldsymbol{\Xi}(\rho)=\boldsymbol{A}-\rho\boldsymbol{B}$$



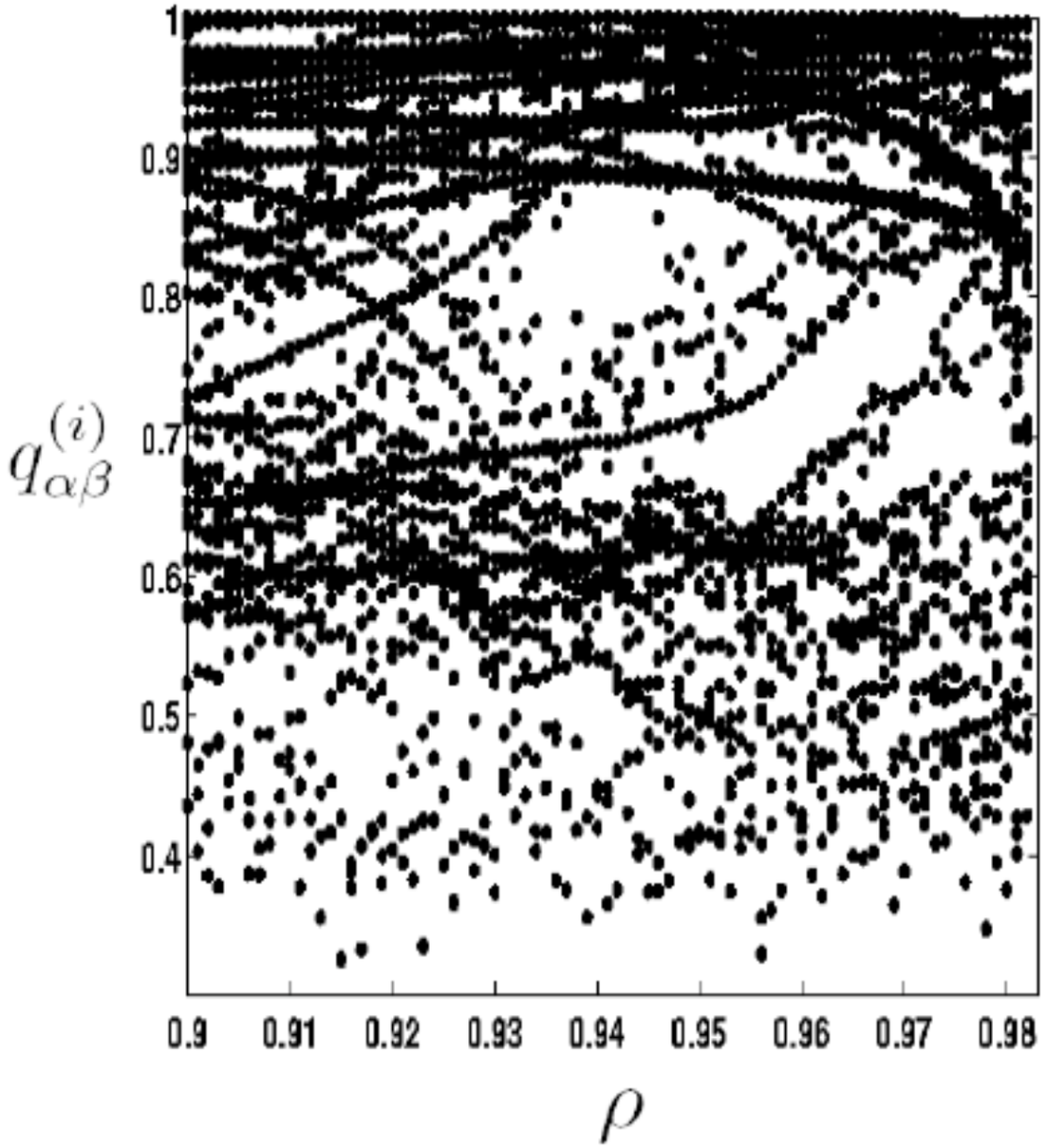
individual fluxes

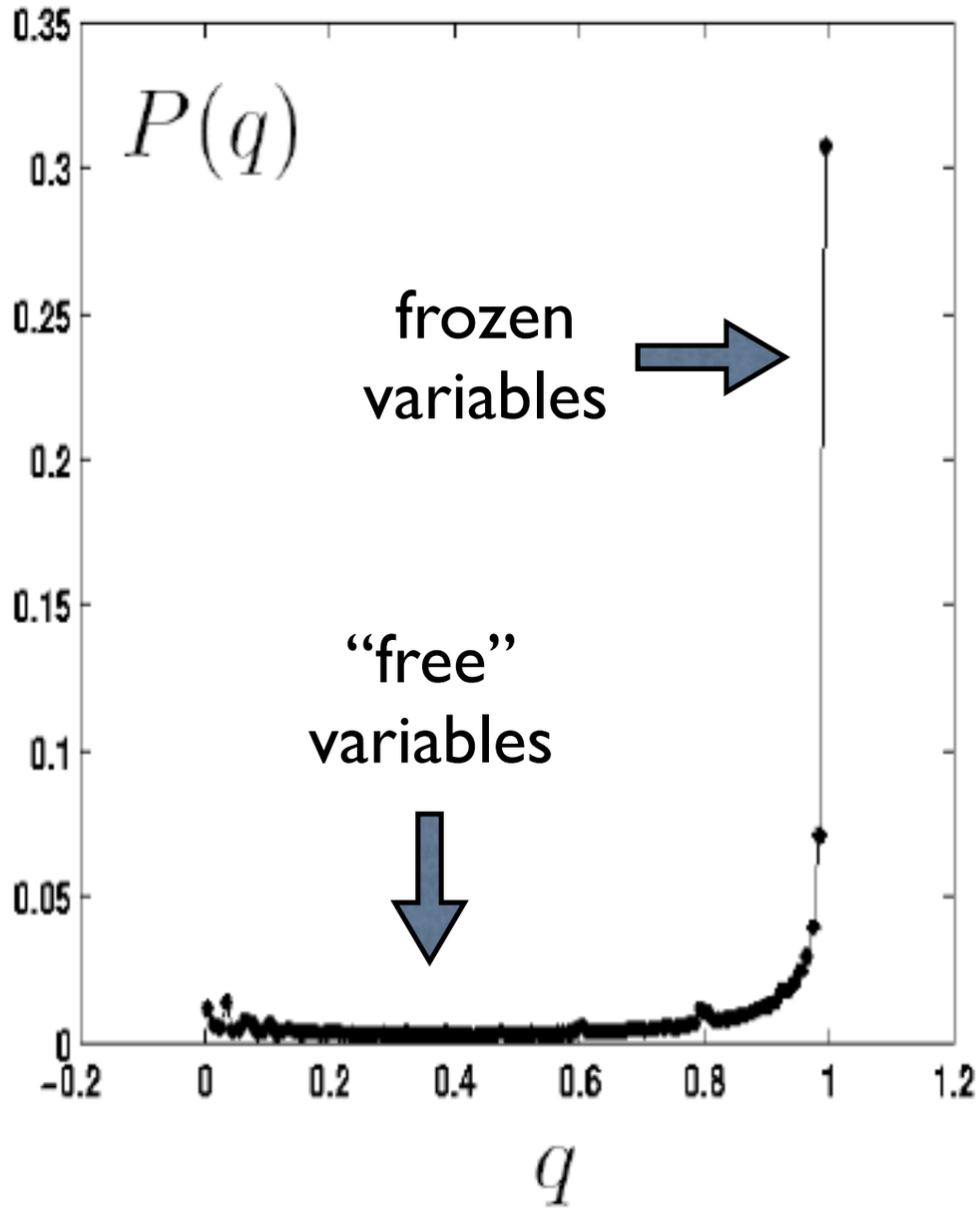


note: low glucose uptake

"shape" of solution space

$$q_{\alpha\beta}^{(i)} = \frac{2 s_{i\alpha} s_{i\beta}}{s_{i\alpha}^2 + s_{i\beta}^2} \qquad (\alpha, \beta = \text{solutions})$$





Biophysical Journal Volume 85 July 2003 16–26
Iman Famili and Bernhard O. Palsson
Department of Bioengineering, University of California San Diego, La Jolla, California 92093-0412 USA

conserved pools of metabolites : groups G of reagents such that

$$\sum_{\mu \in G} (a_i^\mu - b_i^\mu) = 0 \quad \Rightarrow \quad \begin{cases} \rho^\star \leq 1 \\ c^\mu = 0 \quad \forall \mu \in G \end{cases}$$

8) 697, 699 --> *tma(e), tmao(e)*(solo input) {**2 react**: 641, 642}

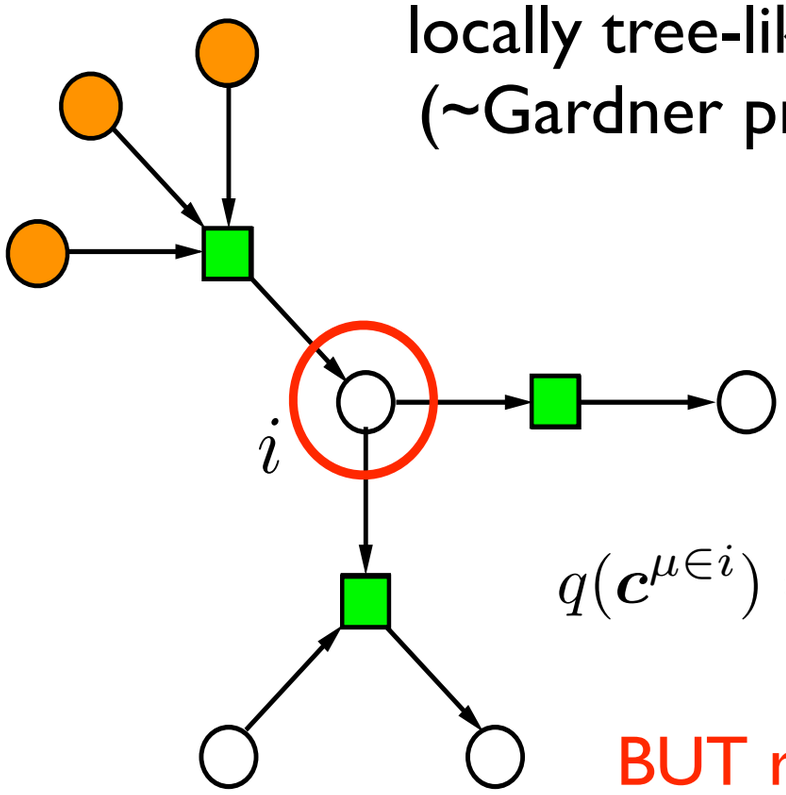
h[e] + mql8[c] + tmao[e] --> h2o[e] + mqn8[c] + tma[e]	Oxidative phosphorylation
2dmmql8[c] + h[e] + tmao[e] --> 2dmmq8[c] + h2o[e] + tma[e]	Oxidative phosphorylation

34) 146, 147, 148, 153, 208, 209, 210 --> *adocbi, adocbip, adocbl, agdpcbi, cbi*(puo' solo input), *cbl1, cbl1(e)*(solo input) {**6 react**: 304, 305, 308, 310, 311, 750}

[c]atp + cbi + h2o <==> adocbi + pi + ppi	Cofactor and Prosthetic Group Biosynthesis
[c]atp + cbl1 + h2o <==> adocbl + pi + ppi	Cofactor and Prosthetic Group Biosynthesis
[c]agdpcbi + rdmbzi --> adocbl + gmp + h	Cofactor and Prosthetic Group Biosynthesis
[c]adocbi + atp --> adocbip + adp + h	Cofactor and Prosthetic Group Biosynthesis
[c]adocbip + gtp + h --> agdpcbi + ppi	Cofactor and Prosthetic Group Biosynthesis
atp[c] + cbl1[e] + h2o[c] --> adp[c] + cbl1[c] + h[c] + pi[c]	Transport, Extracellular

[De M, Martelli, Monasson, JSTAT 2007]

Theory : model on a locally tree-like graph (~Gardner problem)



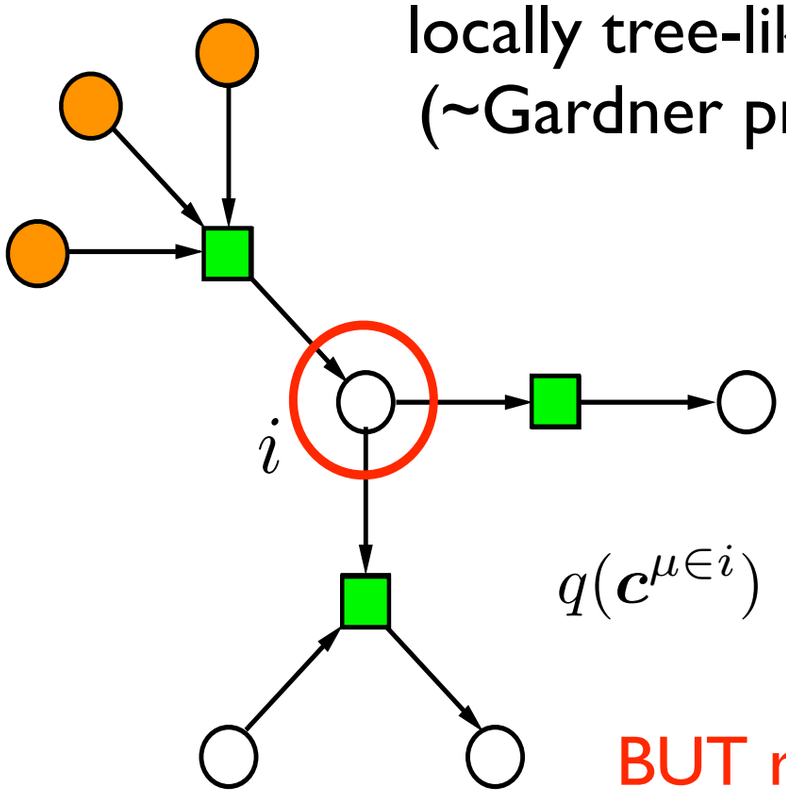
$$q(\boldsymbol{c}^{\mu\in i}) \neq \prod_{\mu\in i} q^{\mu}(c^{\mu})$$

BUT removing i

$$q_{[i]}(\boldsymbol{c}^{\mu\in i}) = \prod_{\mu\in i} q^{\mu}_{[i]}(c^{\mu})$$

Theory : model on a
locally tree-like graph
(~Gardner problem)

[De M, Martelli, Monasson, JSTAT 2007]



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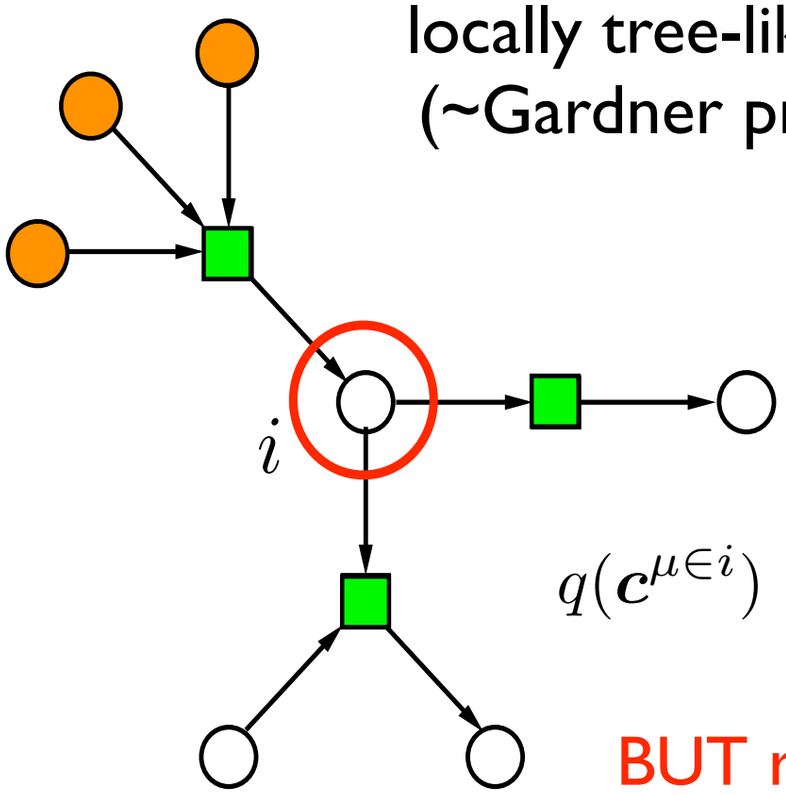
BUT removing i

$$q_{[i]}(\boldsymbol{c}^{\mu\in i}) = \prod_{\mu\in i} q^{\mu}_{[i]}(c^{\mu})$$

$$\Rightarrow \quad q^{\mu}_{[i]}(c^{\mu}) = \mathrm{Tr}^{[i]}_{\boldsymbol{s}_{j\in\mu}} \left[\prod_{j\in\mu}^{[i]} p_j^{[\mu]}(s_j)\right] \delta\left[c^{\mu} - \sum_{j\in\mu}^{[i]} s_j(b_j^{\mu} - \rho a_j^{\mu})\right]$$

Theory : model on a locally tree-like graph (~Gardner problem)

[De M, Martelli, Monasson, JSTAT 2007]



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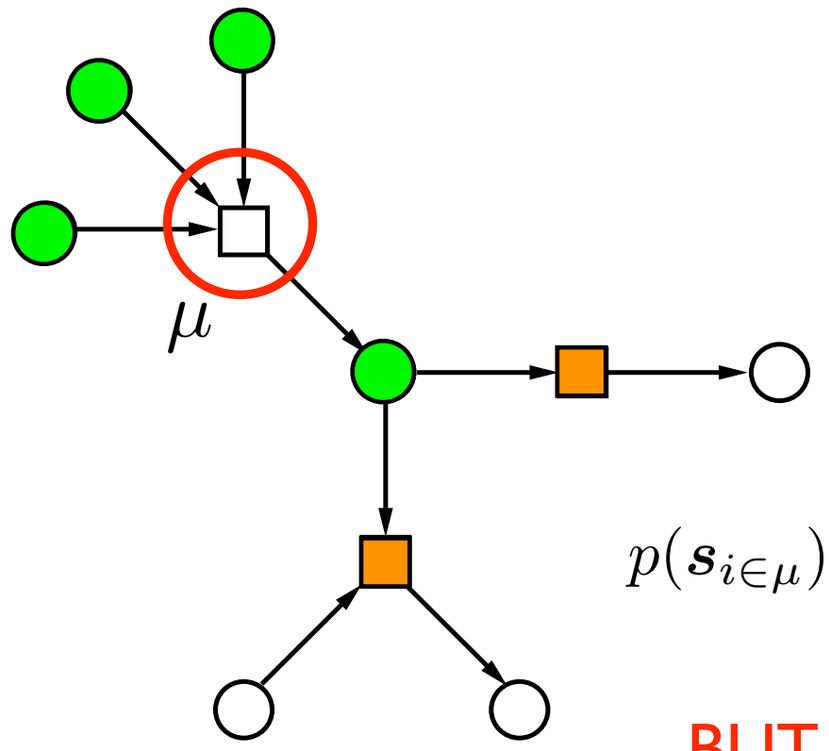
BUT removing i



$$p(\boldsymbol{s}_{i\in\mu}) \neq \prod_{i\in\mu} p_i(s_i)$$

BUT removing

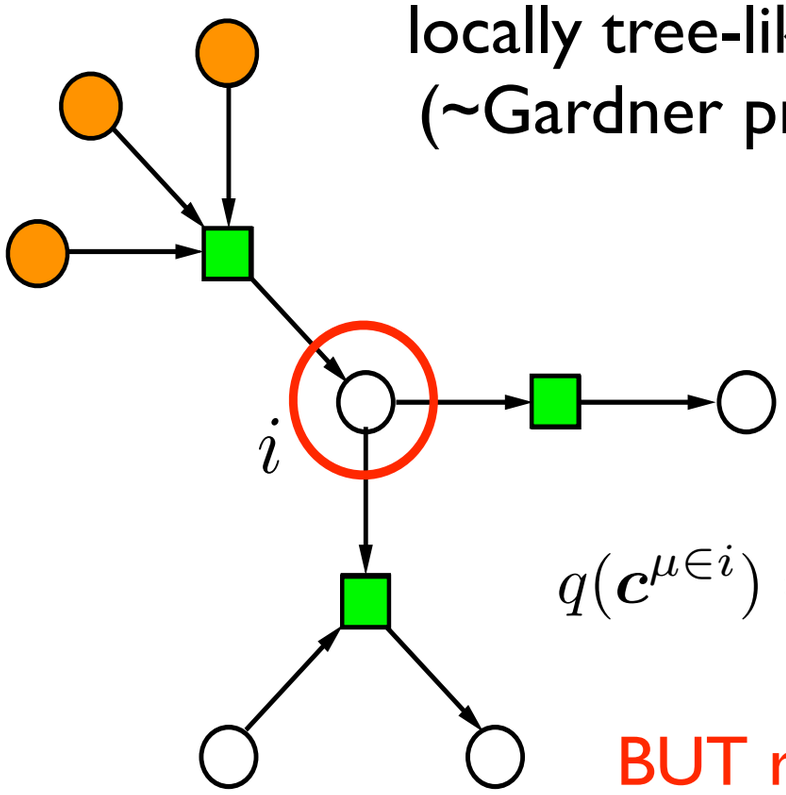
$$q_{[i]}(\boldsymbol{c}^{\mu\in i}) = \prod_{\mu\in i} q^{\mu}_{[i]}(c^{\mu})$$

$$p^{[\mu]}(\boldsymbol{s}_{i\in\mu}) = \prod_{i\in\mu} p_i^{[\mu]}(s_i)$$

$$\Rightarrow \quad q^{\mu}_{[i]}(c^{\mu}) = \mathrm{Tr}^{[i]}_{\boldsymbol{s}_{j\in\mu}} \left[\prod_{j\in\mu}^{[i]} p_j^{[\mu]}(s_j)\right] \delta\left[c^{\mu} - \sum_{j\in\mu}^{[i]} s_j(b_j^{\mu} - \rho a_j^{\mu})\right]$$

Theory : model on a locally tree-like graph (~Gardner problem)

[De M, Martelli, Monasson, JSTAT 2007]



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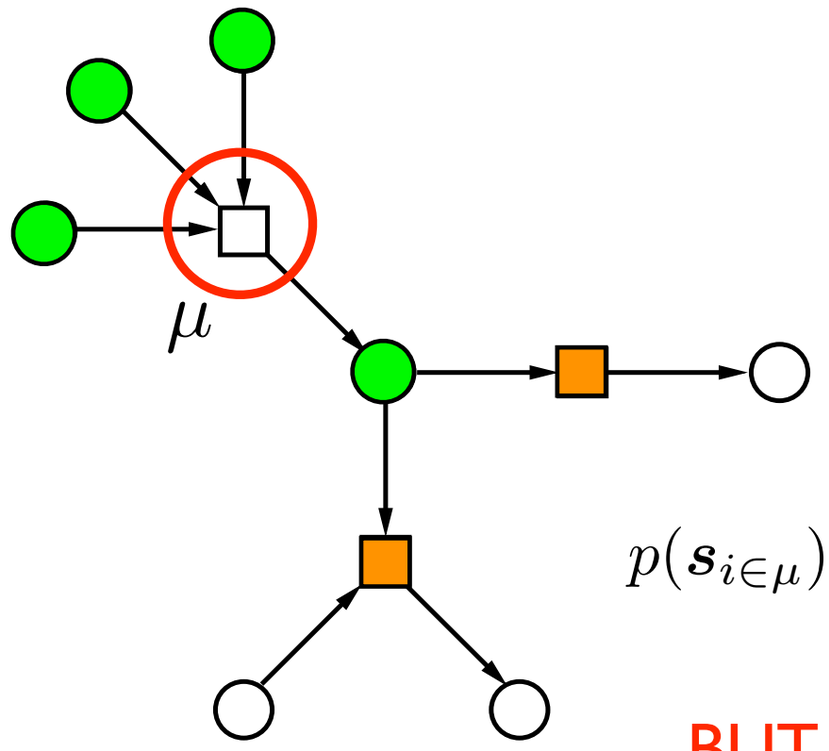

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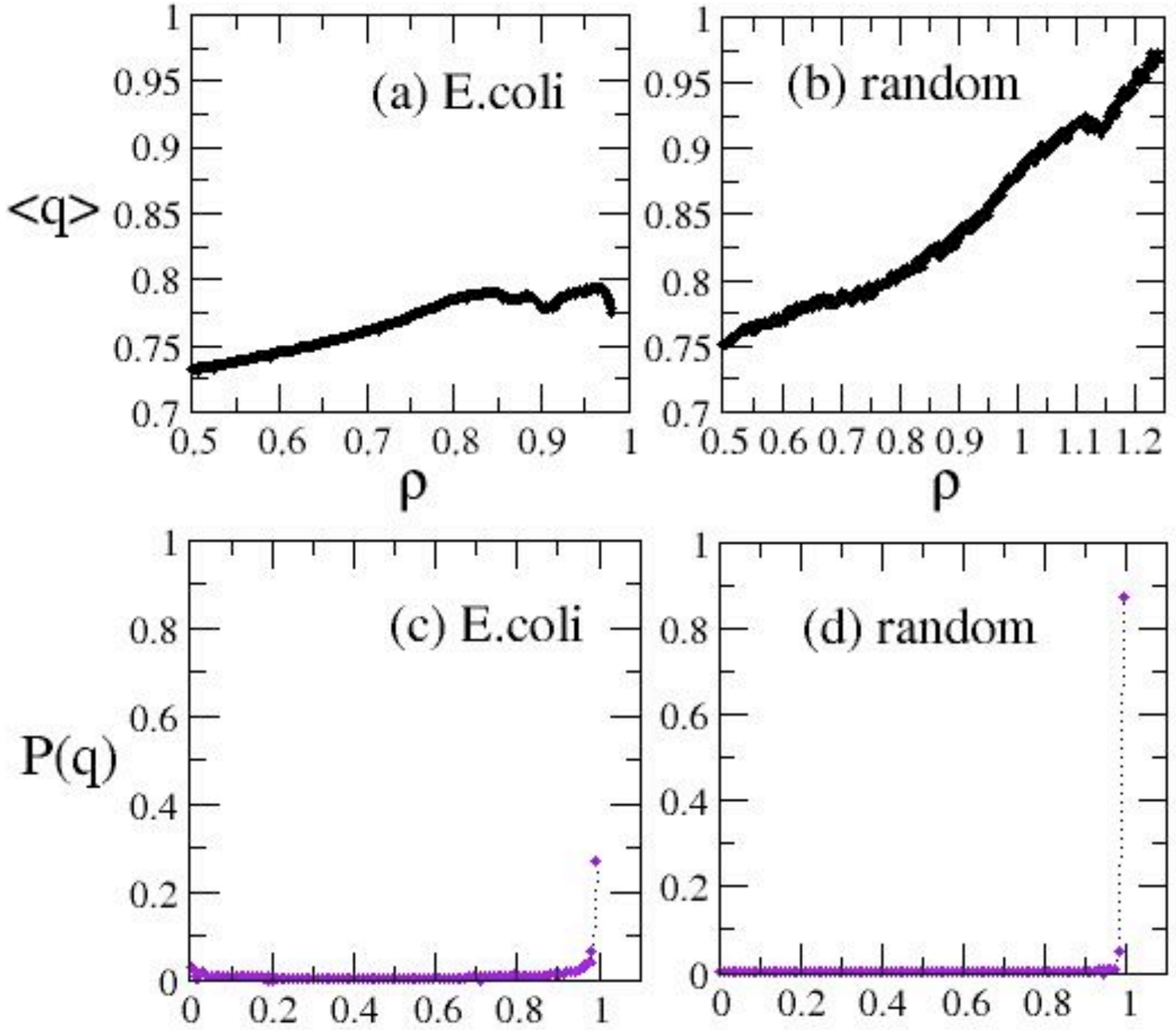
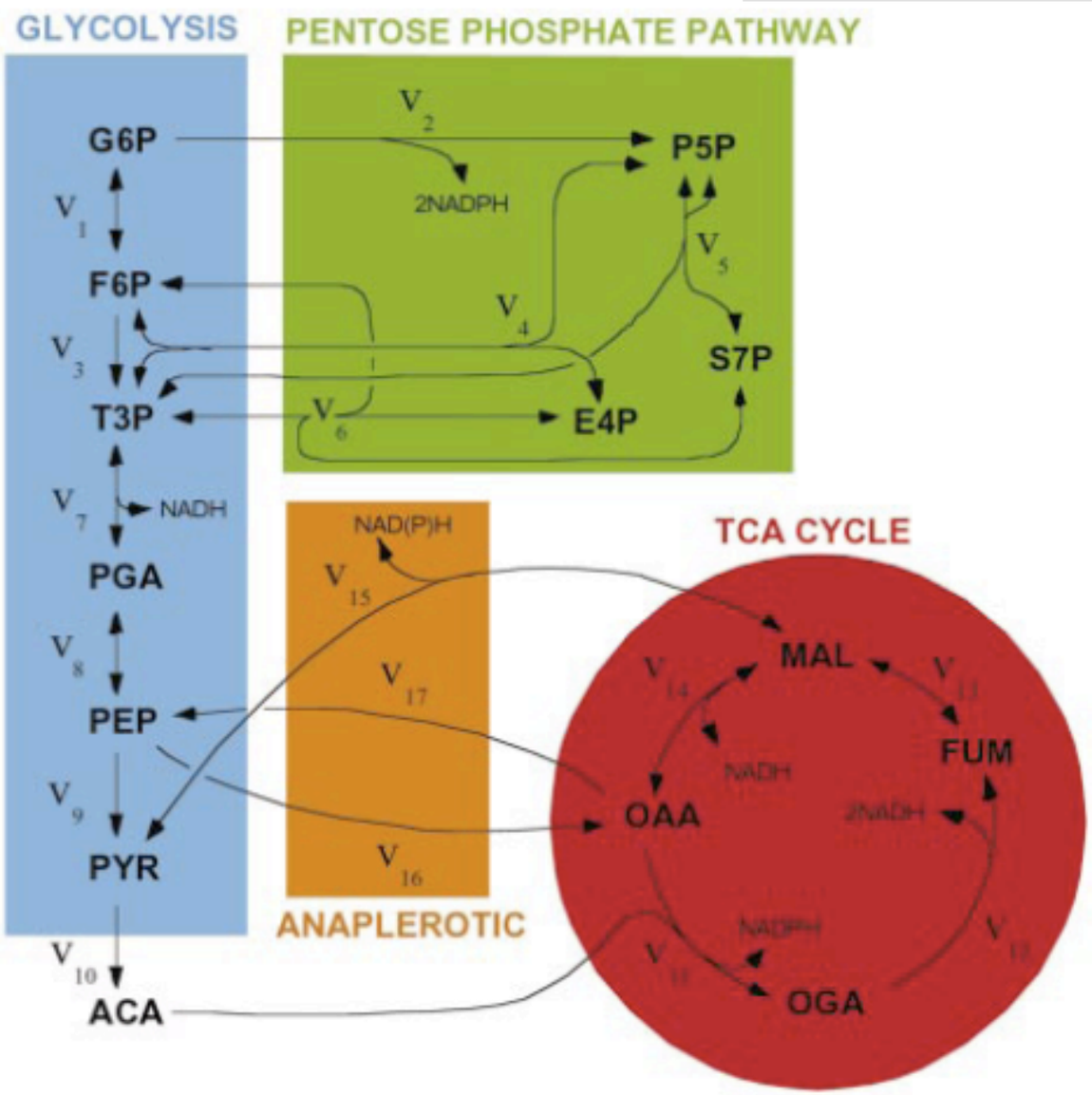
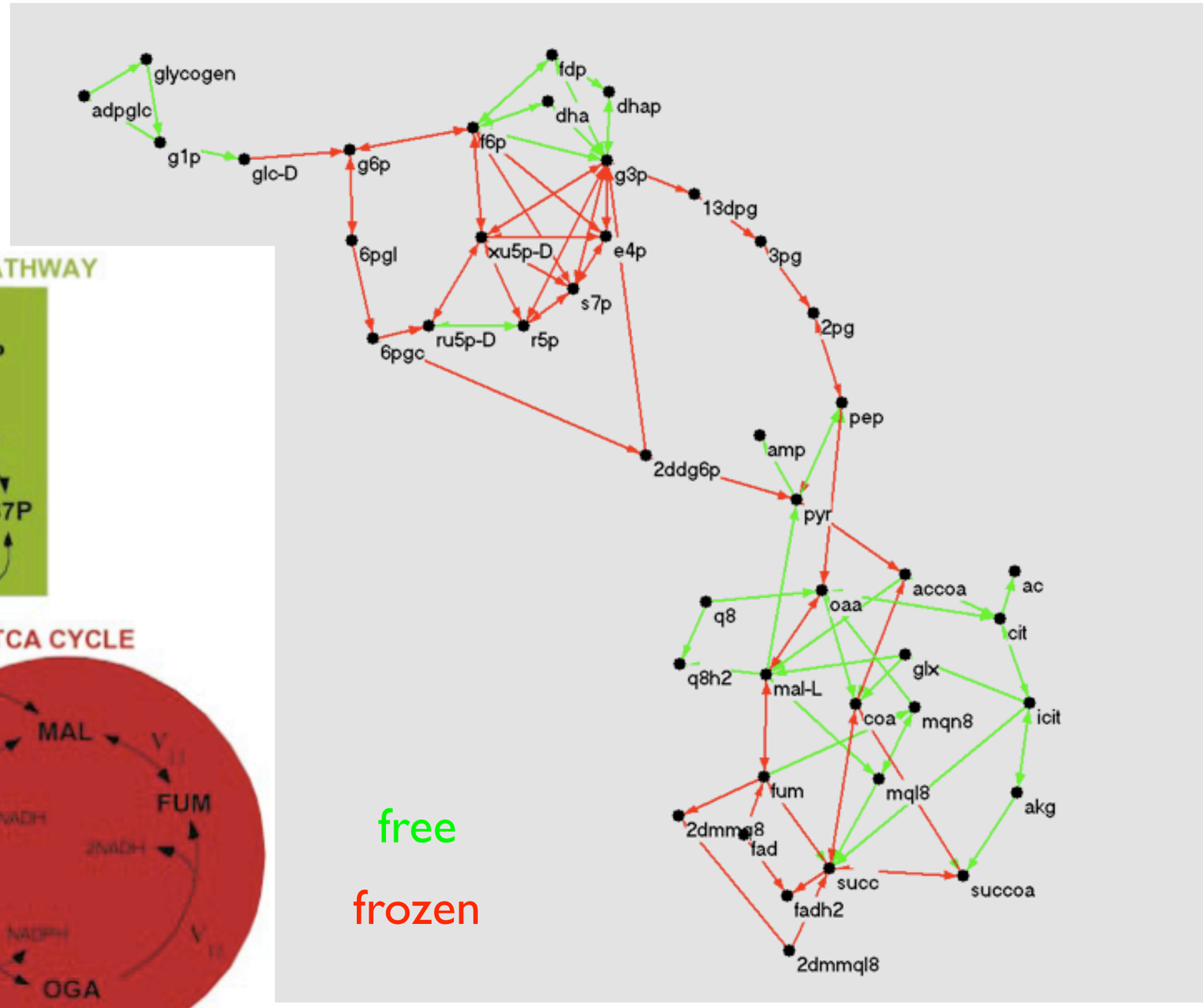
$$\Rightarrow \quad p_i^{[\mu]}(s_i) = \frac{1}{Z_s} \mathrm{Tr}^{[\mu]}_{\boldsymbol{c}^{\nu\in i}} \left[\prod_{\nu\in i}^{[\mu]} q^{\nu}_{[i]}(c^{\nu})\right] e^{-\beta \sum_{\nu\in i}^{[\mu]} \Theta\left[-c^{\nu}_{[i]} - s_i(b_i^{\nu} - \rho a_i^{\nu})\right]}$$

real vs random networks



are frozen fluxes topologically relevant?
e. coli's central metabolism

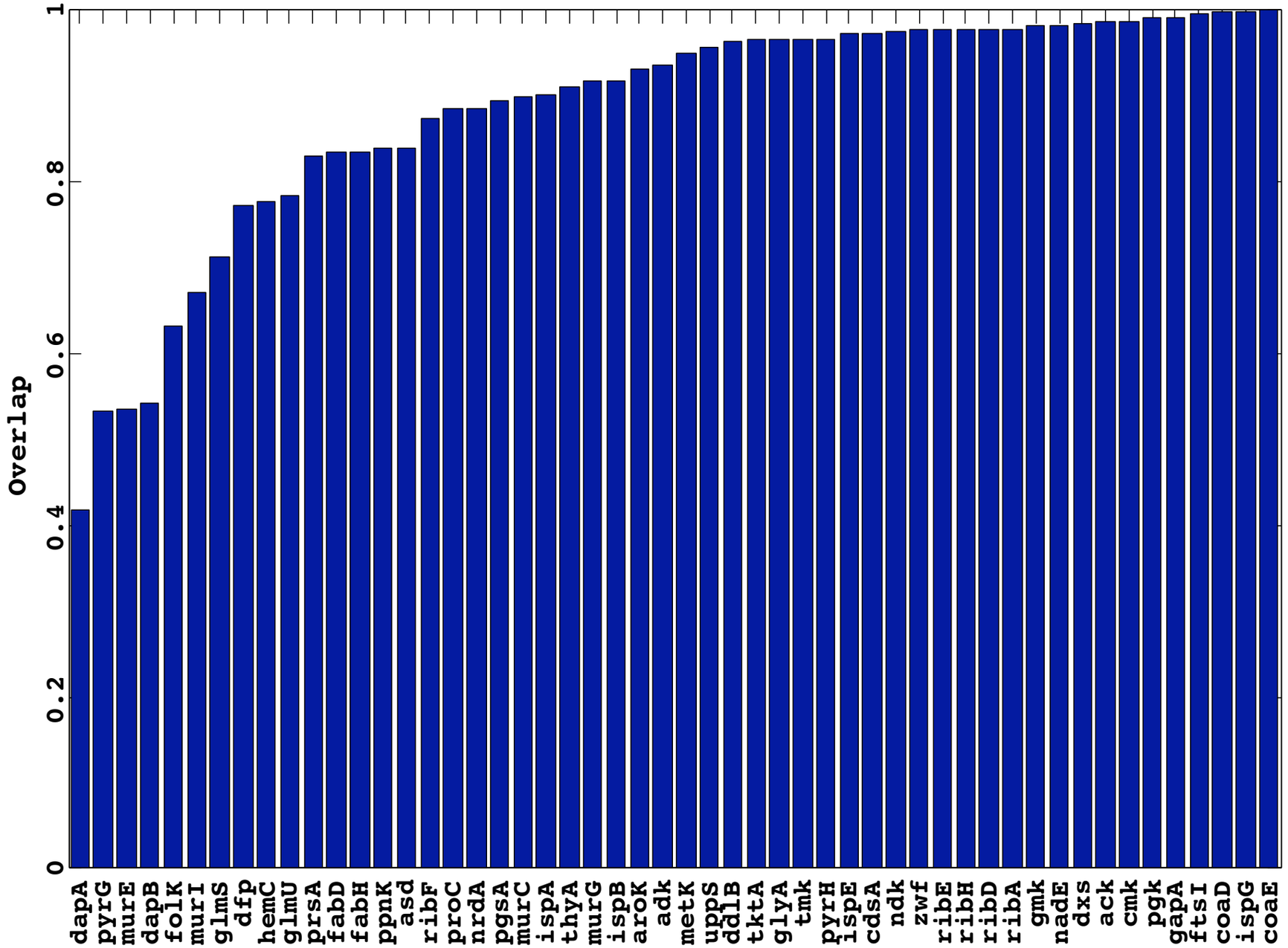




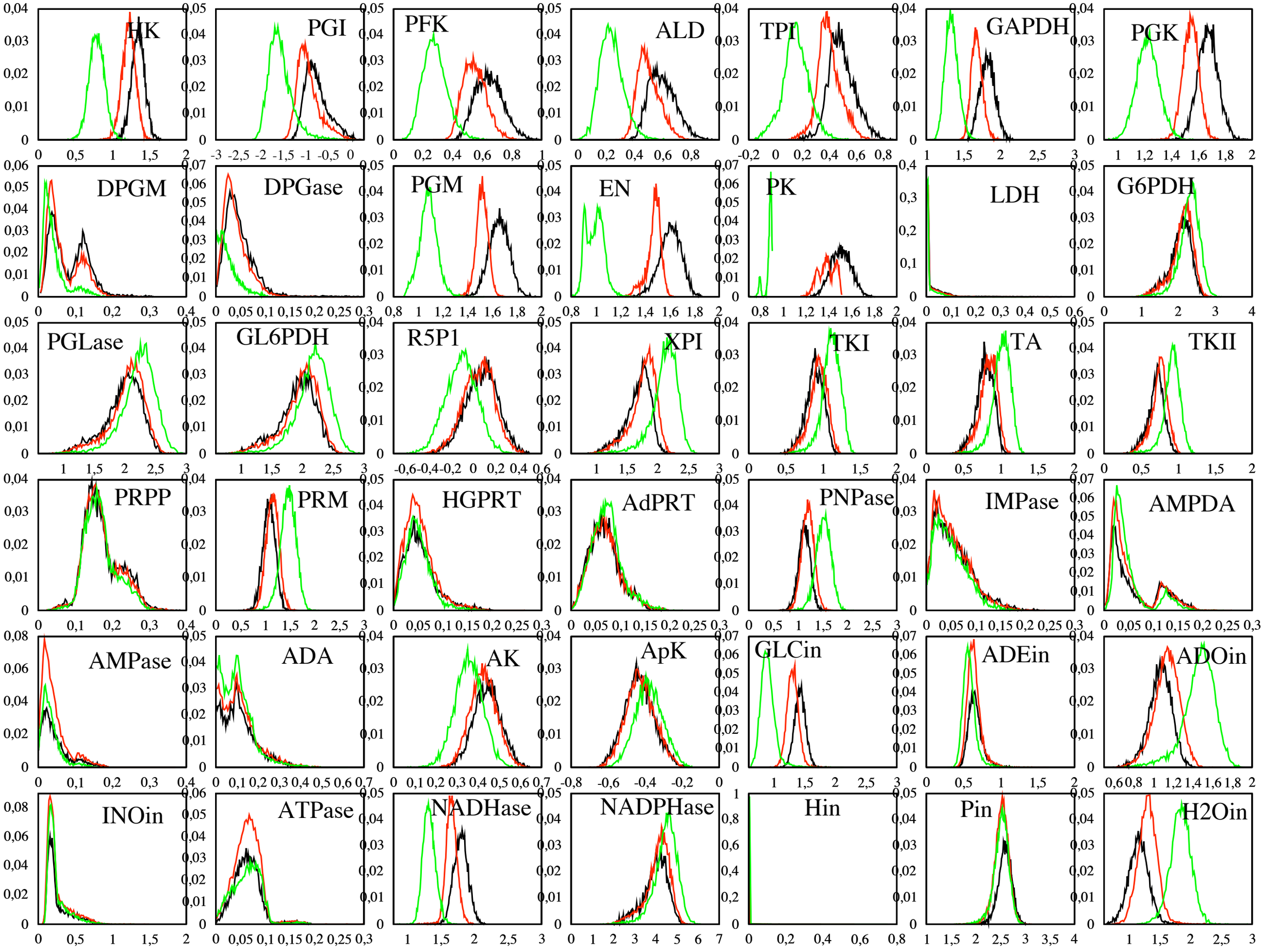
free

frozen

are frozen fluxes relevant?



gene essentiality list from Gerdes *et al.* J. Bacteriology **185** 5673 (2003)


HK
PGI
PFK
ALD
TPI
GAPDH
PGK
DPGM
DPGase
PGM
EN
PK
LDH
G6PDH
PGLase
GL6PDH
R5P1
XPI
TKI
TA
TKII
PRPP
PRM
HGPRT
AdPRT
PNPase
IMPase
AMPDA
AMPase
ADA
AK
ApK
GLCin
ADEin
ADOin
INOin
ATPase
NADHase
NADPHase
Hin
Pin
H2Oin

People

- Daniele Granata (Roma)
- Carlotta Martelli (Roma/Yale)
- Francesco Massucci (Roma/London)
- Remi Monasson (Paris ENS/Rockefeller)
- Matteo Marsili (Trieste)
- Isaac Perez Castillo (London)
- Alfredo Braunstein (Torino)
- Andrea Pagnani (Torino)
- Roberto Mulet (La Habana)

Rome group

- Andrea Cavagna
- Irene Giardina
- Luca Leuzzi
- Enzo Marinari
- Giorgio Parisi
- Federico Ricci Tersenghi
- Miguel A. Virasoro

- Palsson group (San Diego) : gcrg.ucsd.edu
- Sauer group (Zurich) : www.imsb.ethz.ch/researchgroup/sauer
- Segre' group (Boston U) : prelude.bu.edu
- Stoichiometric matrices

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